

ANNUAL REPORT
OF
PROGRAM ACTIVITIES
NATIONAL INSTITUTE OF DENTAL RESEARCH
Fiscal Year 1981
Parts IV, V, VI

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service National Institutes of Health

PART IV

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

INTRAMURAL RESEARCH

October 1, 1980 - September 30, 1981

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Compiled By

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

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1981
pt. 4-6

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Report of the Microbial Systematics Section

National Institute of Dental Research

The Microbial Systematics Section is charged with establishing a data bank for information describing diverse strains of microorganisms. Special emphasis is placed on the human oral microbiota. For this purpose, collaborative projects are on-going with microbiologists distributed throughout the world.

At present there are tens of thousands of scientists, physicians, public health personnel, and others involved in some aspect of microbiology. The number of microbial strains isolated, characterized, and (in many cases) preserved, by individuals runs into the millions. Hundreds of millions of bits of information have been developed on these strains. However, these data are not resident in a single, centrally located system, permitting rapid and efficient utilization. Because of the large volume of information involved and because, in several applications such as classification and identification, mathematical manipulations of the data are required, electronic processing of these data is necessary.

In collaboration with personnel of the American Type Culture Collection, the Food and Drug Administration; the Centers for Disease Control, the Veteran's Administration and numerous academic microbiologists, strain data are being entered into the data bank which provides such services as: data on specific organisms and/or groups of organisms, location of strains with special characteristics, identification of unknown isolates, cluster analysis definition of parameters of taxa, data management and report writing aids for research purposes, aids in quality control of tests, methods, and laboratories, and communication of data via common format.

Data files of primary data on a large number of microorganisms found in the oral cavity and related types are established. These files provide a resource for asking both ecological and epidemiological questions of interest in dental research.

Programs have been developed and tested to enter, retrieve, and analyze the data in a variety of ways for epidemiological, diagnostic, taxonomic, ecological, etc., uses. The long term goal is to establish a world-wide data bank at a series of cooperating centers. As experience grows, better programs are being designed and implemented.

The system originally developed for bacteria is now being expanded to include the yeasts, molds, algae and protozoa. A series of monographs describing the expanded system is in varying stages of publication.

Extensive files of descriptions of filamentous and pleomorphic organisms are being assembled. The files cover all the described types of Mycobacteria, blend into the Nocardia, then through the Actinomycetes (especially a unique set on oral isolates), and finally, Bacterionema. An extensive cooperative study has been initiated to study the oral pleomorphic bacteria (many of which are associated with disease). The study will provide a standard set of well characterized bacteria for the Dental Research community. The data from this

study will be incorporated into the files on pleomorphic organisms. These files are being actively used in collaboration with the submitters of the data as well as numerical taxonomists to revise the badly confused taxonomic relationships of these bacteria. Such revision is necessary to avoid the misidentification (leading to erroneous epidemiological conclusions) which are found in some recent dental research literature.

Other files on non-filamentous oral organisms (streptococci, lactobacilli, veillionella, etc.) are being constructed to study correlations among caries activity, phenetic span of characters, serology, source of isolation, and host descriptions.

One of the long term goals in establishing all these files is the establishment of probability tables to allow computer-aided probabilistic identification of oral isolates. Probability matrices, for on-line identification of bacteria (including Gram negative rods, lactobacilli, streptococci, bacilli, etc.) have been constructed. They are available to research workers for use.

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Walczak, C. A. and Jacobs, B. E.: A Pictorial Query Language for use with any database. *Anal. Chim. Acta/CTO.* In Press.

Hauxhurst, J.D., Krichevsky, M. I., and Altas, R. M.: Numerical taxonomy of bacteria from the Gulf of Alaska. *J. Gen. Microbiol.* 120:131-148, 1980.

Wayne, L. G., Krichevsky, E.J., Love L. L., Johnson, R., and Krichevsky, M. I.: Taxonomic probability matrix for use with slowly growing mycobacteria. *Int. J. Syst. Bacteriol.* 30:528-538, 1980

Daggett, P., Krichevsky, M. I., Rogosa, M., Corliss, J. O., and Girolami, J. P.: Method for coding data on protozoan strains for Computers. *J. Protozool.* 27:353-361, 1980.

Krichevsky, M. I.: Management and querying of morphological, physiological, biochemical, and chromatographic data describing microbial strains. *Anal. Chim. Acta/CTO.* In press.

Wayne, L. G., Good, R. C., Krichevsky, M. I., Blacklock, Z., Chaparas, S. D., Dawson, D., Froman, S., Gross, W., Hawkins, J., Jenkins, P. A., Juhlin, I., Kappler, W., Kleeberg, H. H., Krasnow, I., Lefford, M. J., Mankiewicz, E., McDurmont, C., Meissner, G., Nel, E. E., Pattyn, S. R., Portaels, F., Richards, P. A., Rusch, S., Schroder, K. H., Szabo, I., Tsukamura, M., and Vergman, B.: First report of the cooperative open-ended study of slowly growing mycobacteria (International Working Group on Mycobacterial Taxonomy). *Int. J. Syst. Bacteriol.* 31:1-20, 1981.

PUBLICATIONS (Contd.)

Martin, R., Riley, P.S., Hollis, D.G., Weaver, R.E., and Krichevsky, M.I.: Characterization of some groups of gram-negative nonfermentative bacteria by the carbon source alkalization technique. Int. J. Clin. Microbiol. 14:39-47

Philpot, C.M., Rogosa, M., and Krichevsky, M.I.: Coding of phenotypic data descriptive of selected groups of fungi for entry into computers. In Press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00044-11 ODIR						
PERIOD COVERED October 1, 1980 to September 30, 1981								
TITLE OF PROJECT (80 characters or less) Handling of Microbial Strain Information by Computers								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%;"> <tr> <td style="width: 33%;">Krichevsky, M. I.</td> <td style="width: 33%;">Research Chemist</td> <td style="width: 33%;">NIDR IR</td> </tr> <tr> <td>Love, L. L.</td> <td>Technical Information Spec.</td> <td>NIDR IR</td> </tr> </table>			Krichevsky, M. I.	Research Chemist	NIDR IR	Love, L. L.	Technical Information Spec.	NIDR IR
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COOPERATING UNITS (if any) Please see addendum								
LAB/BRANCH								
SECTION Microbial Systematics Section								
INSTITUTE AND LOCATION National Institute of Dental Research, NIH, Bethesda, Maryland								
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SUMMARY OF WORK (200 words or less - underline keywords) <p> <u>Microbial strain</u> data are being entered into a data bank to provide: data on <u>specific organisms</u>, <u>identification</u> of unknown isolates, cluster analysis definition of parameters of taxa, data management and report writing aids, aids in quality control of tests, methods, and laboratories, and communication of data via common format. Data files of primary data on microorganisms found in the <u>oral cavity</u> and related types are established, providing a resource for asking both <u>ecological</u> and <u>epidemiological</u> questions in dental research. Coding conventions have been developed to relate oral clinical parameters with the incidence and distribution patterns of specific microflora. Thus, indicator organisms for potential and/or on-going disease states can be found for diagnostic purposes. </p> <p> Programs are being developed to enter, retrieve, and analyze the data for epidemiological, diagnostic, taxonomic, ecological, etc. uses. The long term goal is to establish a <u>world-wide</u> data bank at a series of cooperating centers. The original bacterial system is being expanded to include the algae, yeasts, molds and protozoa. </p>								

COOPERATING UNITS: R. Gryder, Food and Drug Administration
F. Benedict, EDRO, Food and Drug Administration
R. Gherna, American Type Culture Collection
B. Brenner, Centers for Disease Control
V. Dowell, Centers for Disease Control
J. Brooks, Centers for Disease Control
L. Wayne, Veterans Administration
V. Sutter, Veterans Administration
R. Atlas, University of Louisville
S. Socransky, Fosyth Dent Center
M. Newman, UCLA
S. Holt, University of Massachusetts

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00250-04 ODIR									
PERIOD COVERED October 1, 1980 to September 30, 1981											
TITLE OF PROJECT (80 characters or less) Algorithms for Microbial Systematics											
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SUMMARY OF WORK (200 words or less - underline keywords) <p>Algorithms are being developed and tested for aiding in numerical taxonomy of feature by strain matrices too large to be analyzed by existing programs Both segmentation and heuristic approaches are being investigated.</p> <p>A program is being designed to compare and evaluate methods and/or laboratories when characterizing the same set of strains. The usual statistical packages are not usual because of the predominantly binary (i.e., discontinuous) nature of the data. The algorithm will allow comparison of tests or laboratories at the levels of individual strain (with replicable determinations), species, genus, and overall set for determination of test method equivalences and/or inter-laboratory consistency.</p> <p>Computer graphic algorithms are being tested to aid microbiologists in visualizing individual similarities as well as heirarchical group memberships among strains.</p>											

ANNUAL REPORT OF THE LABORATORY OF BIOCHEMISTRY
NATIONAL INSTITUTE OF DENTAL RESEARCH
1980 - 1981

The Laboratory of Biochemistry contains three Sections, the Proteoglycan Chemistry Section, the Enzyme Chemistry Section and the Protein Chemistry Section. All are of similar size and composition. Laboratory personnel total about 25 with a ratio of research to support staff of about 2:1. Within the research staff the ratio of temporary (postdoctoral fellows and visitors) to tenure staff is also about 2:1. These figures have not changed significantly over the past several years. Of the temporary scientists about two-thirds are supported by mechanisms (mainly postdoctoral fellowships) that do not count against our position ceiling. This value has been slowly increasing and will likely continue to, if we are to maintain vitality.

A change this year has been the assignment of the Chief, Proteoglycan Chemistry Section to Australia on "sabbatical," for one year. His program has continued to be active in his absence.

The size of the Laboratory programs has been limited largely by our position ceiling and our ability to recruit through other mechanisms. However, space has now become equally limiting. Measurements of program size in practice should also include collaborative arrangements. All of the scientific staff collaborate closely with other scientists within and outside NIDR and NIH, sometimes with several different groups. In this manner productivity is mutually increased. In addition, we utilize some space in Building 2 (NIAMDD) where the nuclear magnetic resonance (nmr) instrumentation is located. We also have access to electron microscope facilities in the Laboratory of Biological Structure, NIDR. Planning for new joint electron microscope facilities is underway, but they will not be available for at least a year.

The product produced by the Laboratory is, of course, original research in several areas of biochemistry related to normal biological function and to disease. The unifying theme is molecular structure and function. In addition to laboratory research, senior personnel participate in a variety of other professional activities of broad importance to science including national and international meetings, reviewing of manuscripts for various scientific journals, evaluating applications for granting agencies and foundations, teaching in the Graduate School at NIH, lecturing to groups within and outside NIH, serving on committees, and organizing meetings. Increasing emphasis in recent years on management responsibilities also takes time and effort of Laboratory personnel. Indeed, this past year has seen a marked increase in time given to administration, particularly in the areas of personnel and travel.

To produce original research is, however, the primary effort of the Laboratory. Progress during the past year is summarized below according to Section.

Proteoglycan Chemistry Section

Proteoglycans are complex macromolecules which contain glycosaminoglycans and often other oligosaccharides covalently attached to distinct core proteins. They are critical structural elements of connective tissue. For example: (a) cartilage proteoglycans directly influence shape and form of the developing skeleton and provide the resiliency and resistance to compressive load required for proper physical function of adult cartilages; (b) corneal proteoglycans are essential components for maintaining the normal, highly organized matrix of the stroma and for transparency of the tissue; (c) proteoglycans are important constituents of basement membranes which serve as filtration barriers in kidney and are essential for morphogenesis in branching epithelial systems.

The Proteoglycan Chemistry Section continues to focus on structure and biosynthesis of cartilage proteoglycans, and to collaborate with other programs primarily interested in proteoglycans in other tissues including cornea, kidney glomeruli and aortic smooth muscle. This past year, utilizing chondrocyte cultures, immunological methods have been used to identify and isolate the newly synthesized core protein prior to biosynthetic addition of glycosaminoglycans. The structures and general locations of other complex carbohydrates on the completed proteoglycan, namely the O-linked oligosaccharides related to keratan sulfate and the N-linked oligosaccharides, have also been determined. The data indicate that the core protein already contains N-linked oligosaccharides in early stages of processing before glycosaminoglycans are added. Addition of O-linked oligosaccharides and glycosaminoglycan chains occurs later at about the same time. Sulfation in the Golgi is the last step. Information about how these processes are regulated is necessary for understanding both normal cartilage function and debilitating cartilage diseases such as osteoarthritis and rheumatoid arthritis.

Less is understood about proteoglycans of other tissues, but it is becoming increasingly more apparent that they vary widely in kind and relative amounts of polysaccharide and protein, and in size and form. For example, granulosa cells make a proteoglycan with only about 20 glycosaminoglycan chains but about 350 O-linked oligosaccharides.

Enzyme Chemistry Section

The study of the transglutaminases was taken up by the group a number of years ago primarily as an interesting subject to study enzyme mechanisms. Until relatively recently it was thought that the chief physiological function of the transglutaminases was one of catalyzing ϵ -(γ -glutamyl)lysine crosslinks between protein molecules for the purpose of maintaining gross forms of structure and limiting degrees of extensibility. Fibrin stabilization is the prototype. It is now evident, partially as a consequence of findings made here, that these enzymes catalyze other important biological reactions, among which are cross-bridging of protein molecules

through polyfunctional amines and incorporation of polyamines and biogenic amines into specific cellular proteins, and that the role of the transglutaminases in regulatory processes may be vitally important. Two recent reports provide evidence for this type of function. It has been found elsewhere that the transglutaminase-catalyzed incorporation of putrescine into ornithine decarboxylase, the inducible enzyme responsible for production of putrescine, results in total loss of its activity. This reaction occurs intracellularly presumably as a control mechanism. In a quite different light, other investigators have described a mechanism by which products of a transglutaminase reaction, uteroglobin crosslinked with embryonic surface proteins, serve to protect the embryo against rejection by the mother's immune system during its first days in the uterus. These findings, together with evidence that transglutaminases are involved in interactions between collagen, fibronectin, fibrin and other extracellular and membrane proteins, such as actin and myosin, attest to the importance and relevance of the basic studies underway in the Enzyme Chemistry Section.

This past year emphasis was placed on two aspects of the broad problem. First, attention was focused on the differences in specificity among the transglutaminases with special interest in defining the different enzymes and providing a basis for design of specific inhibitors for use in biological systems. Clear evidence was obtained for large areas of secondary enzyme-substrate interactions estimated to be in the range of 15 or more amino acid residues surrounding substrate glutamines. Differences in these interactions appear to provide the specificity differences among the enzymes. Secondly, cellular mechanisms for catabolism of transglutaminase products were investigated. Evidence was obtained that normal turnover of transglutaminase-modified extracellular proteins involves a series of sequential steps with a final disassembly of the γ -glutamyl linkage, rather than cleavage of this linkage in intact protein molecules.

A new project this year arose from observations made on the metabolism of polyamines, substrates for the transglutaminases. A new and unusual amino acid, hypusine, was found in a low molecular weight cytosol protein present in all growing mammalian cells. Biosynthesis of this amino acid by way of a rather elaborate posttranslational mechanism utilizes a novel pathway of polyamine metabolism and an unique enzymic hydroxylation step. Efforts are underway to determine the cellular function of the single ubiquitous protein containing this rare amino acid.

Protein Chemistry Section

The protein chemist works with the collagen molecule which contains three polypeptide chains in a rod-like triple helix. In vivo, however, collagen is present as an aggregate of molecules arranged in an orderly array, the native fibril (types I, II and III collagen). The major interest in structure is currently at the fibril level: how are molecules arranged and how

are fibrils formed? Fibril structure was thought to be essentially answered several years ago with the five-fold microfibril model. However, a three-dimensional crystal model has appeared that is superior in some respects but not in others. Studies done here support a compromise model, the compressed microfibril model, but in the absence of new data the question is very much controversial. Efforts to obtain new data, primarily by electron microscopy, continue.

Assembly of collagen to make fibrils in vivo is clearly complex. Studies in vitro have been done in an effort to simplify the system. Studies done here support a multistep accretion mechanism as opposed to the more classical nucleation-growth mechanism. Supporting evidence came from studies with normal type I collagen from rat tail tendon. This past year the studies have been extended to type I collagen from lathyrtic rat skin and type II collagen from a rat chondrosarcoma (also lathyrtic). These collagens make fibrils in vitro but under quite different conditions. Higher concentrations and temperatures are needed. A major difference is that the fibrils cannot crosslink, which may affect the kinetics and the nature of the product.

Other studies using mass measurements made by scanning transmission electron microscopy are attempting to determine the structure of an aggregate formed early in assembly. It appears to consist of end-overlapped molecules in bundles of 5-150 molecules and strings up to about 15 molecules long. Its size and shape is consistent with an aggregate characterized earlier by quasielastic light scattering. The overlaps are about 50nm. This structure does not appear to be directly related to fibril structure. It may, therefore, not be an intermediate but rather a byproduct.

A technique that has revolutionized the study of molecular interactions in solid state material including tissue is nuclear magnetic resonance (nmr). Studies in the Protein Chemistry Section in recent years using ^{13}C nmr have shown that collagen molecules in the native fibril are in rapid anisotropic motion about their axes. This motion has been further defined to show that oscillation occurs through an angle of at least 30° at 20°C but motion is frozen at -20°C . In addition, amino acid side chains are in motion. Leucine side chains change conformation at rates of 10^4 s^{-1} at -85°C to 10^6 s^{-1} at 30°C . Thus, interactions between molecules must be fluid but at the same time must be sufficiently restricting to define some degree of three-dimensional order. Future studies will attempt to localize motion to particular regions that may have structural or biological significance.

The same nmr techniques applied to proteoglycans show similar motion in both the polysaccharide and the protein chains that is, however, essentially isotropic. This motion allows rapid changes in shape that must be important to function.

Hemoglobin S, somewhat like collagen, forms a fibrous aggregate in the

deoxygenated state that is responsible for the distortion of red blood cells in sickle cell anemia. The interactions that occur between hemoglobin S molecules in solution and aggregated states can be distinguished by nmr, which thus provides a nondestructive technique to follow the process and to test inhibitors of the transition in red blood cells. In the physiologically relevant region of oxygen saturation (~ 60% to 100% oxygen saturation) polymer is not detectable in heterozygotic erythrocytes (sickle cell trait) whereas polymer is detectable in homozygotic erythrocytes (sickle cell anemia), even at oxygen saturation values >95%. These results are in agreement with the benign nature of sickle trait as contrasted with the pathology of sickle cell anemia and demonstrate the usefulness of the nmr technique as an assay for polymer formation in intact cells.

This brief review shows the Laboratory to have been active and productive in all its programs. If a negative note were to be sought, it would be that some opportunities may have been lost owing to the inability to expand and the lack of flexibility imposed by administrative requirements.

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<table style="width: 100%; border: none;"> <tr> <td style="width: 35%;">Hascall, V.C.</td> <td style="width: 45%;">Chief, Proteoglycan Chemistry Section</td> <td style="width: 10%;">LB</td> <td style="width: 10%;">NIDR</td> </tr> <tr> <td>De Luca, S.M.</td> <td>Senior Staff Fellow</td> <td>LB</td> <td>NIDR</td> </tr> <tr> <td>Kimura, J.H.</td> <td>Senior Staff Fellow</td> <td>LB</td> <td>NIDR</td> </tr> <tr> <td>Thonar, E.J-M.A.</td> <td>Visiting Associate</td> <td>LB</td> <td>NIDR</td> </tr> <tr> <td>Fellini, S.A.</td> <td>NIH Postdoctoral Fellow</td> <td>LB</td> <td>NIDR</td> </tr> <tr> <td>Yanagishita, M.</td> <td>Expert</td> <td>LB</td> <td>NIDR</td> </tr> <tr> <td>Stevens, J.W.</td> <td>Arthritis Foundation Fellow</td> <td>LB</td> <td>NIDR</td> </tr> <tr> <td>Lohmander, L.S.</td> <td>Visiting Associate</td> <td>LB</td> <td>NIDR</td> </tr> <tr> <td>Aaron, R.</td> <td>Guest Worker</td> <td>LB</td> <td>NIDR</td> </tr> <tr> <td>Hassel, J. R.</td> <td>Research Biologist</td> <td>LDBA</td> <td>NIDR</td> </tr> </table>			Hascall, V.C.	Chief, Proteoglycan Chemistry Section	LB	NIDR	De Luca, S.M.	Senior Staff Fellow	LB	NIDR	Kimura, J.H.	Senior Staff Fellow	LB	NIDR	Thonar, E.J-M.A.	Visiting Associate	LB	NIDR	Fellini, S.A.	NIH Postdoctoral Fellow	LB	NIDR	Yanagishita, M.	Expert	LB	NIDR	Stevens, J.W.	Arthritis Foundation Fellow	LB	NIDR	Lohmander, L.S.	Visiting Associate	LB	NIDR	Aaron, R.	Guest Worker	LB	NIDR	Hassel, J. R.	Research Biologist	LDBA	NIDR
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COOPERATING UNITS (if any) D. Lowther, Monash Univ., Victoria, Australia; K. Nakazawa, NEI; Bo Nilsson, NCI; A.R. Poole, Shriners' Children's Hosp., Montreal, Canada; Y. Kanwar, Northwestern Univ., IL; M. Farquhar, Yale																																										
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SUMMARY OF WORK (200 words or less - underline keywords) The purpose of the project is to study the <u>chemical</u> and <u>physical properties</u> of <u>proteoglycans</u> and their <u>biosynthesis</u> . Topics of present interest include: 1) chemistry of proteoglycans isolated from the <u>Swarm rat chondrosarcoma</u> , 2) bio-synthesis of the protein core of proteoglycans and the <u>link proteins</u> by <u>chondrocyte</u> cultures, 3) proteoglycans from ovarian <u>granulosa cells</u> , 4) chem-ical characterization of proteoglycan from fetal <u>bone</u> , 5) chemical character-ization of proteoglycans in <u>fetal cartilage</u> and chondrosarcomas of different degrees of malignancy. The proteoglycan of <u>cartilage</u> is best understood, but increasing knowledge of other proteoglycans shows a wide diversity in size, form and function.																																										

1. Project Description

Background

Cartilage proteoglycans are large macromolecules (M_r of 1-5 million) in which large, but variable, numbers of sulfated polysaccharide chains, chondroitin sulfate (CS) and keratan sulfate (KS), are covalently attached to a core protein. N- and O-linked oligosaccharides are also present. Such a molecular architecture yields macromolecules which occupy large hydrodynamic volumes in solution and which exhibit reversible compressibility, characteristics that help provide cartilages with resiliency and resistance to compressive forces. The core protein of cartilage proteoglycans consists of three distinct regions. One end, referred to as the HA-binding region, has a portion of protein (M_r about 70-90 thousand) which is devoid of glycosaminoglycans and which interacts in a highly specific way with both hyaluronic acid (HA) and a protein (M_r of 45,000) referred to as the "link" protein. These interactions are critical for the organization of proteoglycans into aggregate complexes, the predominant form of the proteoglycans in the tissue matrix. Adjacent to the HA-binding region is a portion of the core protein, referred to as the KS-enriched region (M_r about 25-40 thousand), which contains an average of about 65% of the KS chains but less than 10% of the CS chains present in the intact molecules. Distal to the HA-binding region is a portion of the core protein, referred to as the CS-enriched region. This latter region has a variable molecular weight (from a few thousand to 200,000) and contains more than 90% of the CS chains but less than 35% of the KS chains present in the intact molecules. The variable length of this region appears to be proportional to the number of CS chains present on any individual proteoglycan molecule. The average cartilage proteoglycan molecule contains about 80 CS chains (average M_r about 20,000 per chain) and 100 KS chains.

Proteoglycans are found in all connective tissues. As our understanding of cartilage proteoglycans increases, the knowledge and experience gained are being applied to proteoglycans of other tissues. They all have the same basic chemistry, but differ widely in size, relative proportions of protein, glycosaminoglycan and oligosaccharide and, of course, in biological function.

Within NIDR, this program collaborates with: 1) Dr. Dennis Torchia of this laboratory in studies relating to nmr of hyaluronic acid-binding region prepared from rat chondrosarcoma (Project # Z01 DE 00157-06), 2) Dr. John Termine, Laboratory of Biological Structure, in studies on the proteoglycans of fetal bone (Project # Z01 DE 00074-09).

The following sections describe our ongoing projects.

1. Characteristics of proteoglycans isolated from the Swarm rat chondrosarcoma.

Treatment of proteoglycan aggregates with clostripain cleaves the proteoglycan core protein allowing the removal of the CS-enriched region from a ternary complex consisting of the HA-binding region of the core protein, link protein, and hyaluronic acid. Dissociation of the complex by 4M guanidine HCl followed by molecular sieve chromatography under dissociative conditions allows the separation of the HA-binding region from the link protein. Both the complex and its purified components were used in several studies as follows:

- (a) During the development of an enzyme-linked immunoassay (ELISA) for the HA-binding region and link protein, it was found that the antigenicity of the purified link protein increased up to 4-fold when other components of the aggregate proteoglycan monomer of hyaluronate were present. This indicated that additional antigenic determinants were exposed when the link protein bound to either proteoglycan or HA. The increase in antigenicity was consistent with a tetrameric form of link protein as was suggested by studies done in collaboration with Dr. A. Robin Poole using isoelectric focusing and rocket immunoelectrophoresis. These studies further suggest the presence of more than one antigenic species of link protein and proteoglycan in the rat chondrosarcoma.
- (b) Studies were initiated in collaboration with Dr. Dennis Torchia's program of this laboratory in examining the hyaluronic acid-binding region by NMR for alterations produced by its interaction with other components of the aggregate.
- (c) Peptide mapping of purified hyaluronic acid binding region by protease treatment followed by two dimensional separation on cellulose plates first by thin layer chromatography and then by electrophoresis was initiated as a preliminary step toward sequencing the protein and for use in the identification of this region of the core protein in biosynthetic studies.

2. Characteristics of proteoglycans synthesized in culture by chondrocytes from the Swarm rat chondrosarcoma.

- (a) Timing and subcellular sites of carbohydrate addition to the core protein precursor to cartilage proteoglycan:

In one study, the rate of venting of ^3H -radioactivity into newly synthesized proteoglycan was examined using ^3H -glucosamine as a precursor. The relative amounts of label in chondroitin sulfate and O-linked oligosaccharide were compared for labeling times between 15 and 420 min. The ratio of label in chondroitin sulfate to O-oligosaccharide was constant, 36-40, at all times,

indicating that the O-oligosaccharides were added to the core protein at, or nearly at, the same time as the glycosaminoglycan chains.

In other studies, cultures of chondrocytes from the rat chondrosarcoma were incubated with ^3H -mannose, ^3H -glucose, or ^3H -glucosamine for 8h to uniformly label the intracellular pool of core protein precursor to chondroitin sulfate proteoglycan. The labeled core protein was then isolated by using carrier proteoglycan aggregate to form mixed aggregates with the functional core protein allowing the low buoyant density core protein to be recovered from the high buoyant density proteoglycan aggregate fraction on CsCl density gradients. Subsequent dissociative CsCl centrifugation and column chromatography allowed the separation of the core protein precursor from completed proteoglycans. Analysis of the labeled monosaccharides suggested that (1) the N-linked mannose oligosaccharide was present already processed but lacking the terminal sugars at its nonreducing ends, (2) little if any completed O-linked oligosaccharide was found, consistent with the findings described above, and (3) xylose, the linkage sugar between the core protein and chondroitin sulfate chains, was present but was not linked to any great extent to galactose, the next sugar in the linkage region.

Subcellular fractionation by discontinuous sucrose gradient centrifugation of post mitochondrial supernatants from cell homogenates was used to separate vesicles of rough endoplasmic reticulum from vesicles of smooth membrane containing Golgi and plasma

membrane. After a 2-min pulse of ^{35}S -sulfate, less than 10% of the macromolecular radioactivity was in the rough membrane fraction, which is consistent with sulfation occurring in the Golgi as one of the last steps in proteoglycan synthesis. When cells were labeled with ^3H -serine for 4h prior to subcellular fractionation, nearly 70% of the intracellular core protein (as determined by immunoprecipitation with specific antiserum to hyaluronic acid-binding region) was found in the rough membrane fraction. Conversely, most of the serine in intracellular completed proteoglycan was associated with the smooth membrane fraction and comprised at most 10% of the total intracellular core protein radioactivity. These results suggest that the intracellular core protein precursor described in the previous section was derived from the rough endoplasmic reticulum, a suggestion which was supported by examination of the subcellular distribution of ^3H -mannose and ^3H -glucose labeled core protein, >60% of the mannose label but only 25% of the glucose was in the rough membrane fraction.

(b) Effect of tunicamycin on proteoglycan aggregate formation:

Tunicamycin was used to inhibit the synthesis of N-linked oligosaccharides in proteoglycan and link protein. ^3H -mannose was used

to monitor N-linked oligosaccharides synthesis. At $\geq 30\mu\text{g/ml}$ tunicamycin, ^3H -mannose incorporation was inhibited by $>95\%$. Proteoglycan synthesis was less affected $\sim 25\%$ inhibition as indicated by ^3H -glucosamine labeling. The amount of proteoglycan aggregate in the culture medium, however, decreased by up to 40% . Although the proteoglycan and link protein contained less than 10% of the N-linked oligosaccharide, both were functional as shown by reaggregation studies. The major alteration was a reduction in the relative amount of hyaluronic acid in the culture medium although the total hyaluronic acid synthesis remained constant relative to proteoglycan synthesis.

3. Proteoglycans from granulosa cells

The major proteoglycan species synthesized by granulosa cells contains in addition to approximately 20 glycosaminoglycan chains about 350 O-galactosaminyllinked oligosaccharides of similar composition to the O-linked oligosaccharides of cartilage proteoglycan. CsCl density gradient centrifugation, alkaline-borohydride treatment and molecular sieve chromatography were used to isolate these oligosaccharides. Their structure is being determined in collaborative studies by Dr. Bo Nilsson (NCI) using gas-liquid chromatography and mass fragmentation analysis. Work has continued on the synthesis of proteoglycans synthesized by cultured granulosa cells. Emphasis is being placed on the ^{35}S -sulfate-labeled proteoglycans of the cell layer to determine their relationship to the labeled proteoglycans in the culture medium. Kinetic experiments are being done to determine which of the cell layer proteoglycans are precursors of the medium proteoglycans.

4. Chemical characterization of proteoglycan from fetal bone (in collaboration with Dr. John Termine)

Bone slices were sequentially extracted with 4M guanidine.HCl then 4M guanidine-0.5M EDTA. The proteoglycans were isolated by CsCl density gradient centrifugation or DEAE cellulose chromatography. One predominant proteoglycan was found (approximately $2/3$ in the guanidine.HCl and $1/3$ in the guanidine HCl-EDTA extract). It contains 2-4 dermatan sulfate glycosaminoglycan chains, M_r about 40,000, and is about 25% protein. It contains oligosaccharides which give a sialic acid pattern on molecular sieve columns quite similar to that produced by cartilage proteoglycan oligosaccharides as well as those from the follicular fluid proteoglycan. This suggests the presence of both O- and N-linked oligosaccharides.

5. Chemical characterization of proteoglycans in fetal cartilage and chondrosarcomas of different degrees of malignancy (in collaboration with Dr. Lawrence Rosenberg)

These studies were undertaken to examine the hypothesis that the ratio of keratan sulfate to O-linked oligosaccharides, both of which probably share the same linkage region in cartilage proteoglycan, can be used as an indicator of the developmental age of a cartilage. Furthermore, since the proteoglycans made by chondrosarcomas appear to be poorer in keratan sulfate than normal cartilage, proteoglycans from chondrosarcomas of different degrees of malignancy were examined to determine if a reciprocal correlation exists between the degree of malignancy and the ratio of keratan sulfate to O-linked oligosaccharide. Purified proteoglycans were treated with alkaline-borohydride to free the keratan sulfate and O-linked oligosaccharides from the protein core. The amount of sialic acid, the terminal sugar, in keratan sulfate to O-linked oligosaccharide was used as an indicator of the ratio. For fetal cartilage a positive correlation was found for the keratan sulfate: O-linked oligosaccharide ratio, which increased from 0.41 at 129 days of gestation to 0.52 at 241 days. One chondrosarcoma has been examined to date. It contained two distinct regions differing in malignancy. Preliminary data suggest that the low grade hyaline part of the tumor had more keratan sulfate relative to oligosaccharide than did the high grade myxoid region, the ratios being 1.3 and 0.6, respectively.

Significance

Proteoglycans are major structural components of connective tissue. This is most obvious in cartilage where they in part determine the physical properties and form of the tissue and are critical for normal skeletal function and development. Proteoglycans are also found in all other connective tissues, although sometimes only in small amounts. Their role in these tissues is in general not well understood, but is undoubtedly critical to function. We can already gain a general understanding from the diversity of form of proteoglycans attained by varying the amount and kind of protein and polysaccharide.

Proposed Course

The project will continue to investigate such parameters as the physical and chemical properties of proteoglycans, their interactions with other matrix molecules in the organization of an extracellular matrix, the mechanisms involved in their biosynthesis and catabolism, and the changes they undergo during tissue development and aging. A broad approach will be continued emphasizing not only basic physical and chemical studies but also the role of proteoglycans in biological systems.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00001-29 LB									
PERIOD COVERED October 1, 1980 to September 30, 1981											
TITLE OF PROJECT (80 characters or less) Transglutaminases: Specificities, Physiological Functions, and Catabolism of Products											
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Folk, J.E.</td> <td style="width: 33%;">Chief, Enzyme Chemistry Section</td> <td style="width: 33%;">LB NIDR</td> </tr> <tr> <td>Fink, M.L.</td> <td>Staff Fellow</td> <td>LB NIDR</td> </tr> <tr> <td>Park, M.H.</td> <td>Visiting Fellow</td> <td>LB NIDR</td> </tr> </table>			Folk, J.E.	Chief, Enzyme Chemistry Section	LB NIDR	Fink, M.L.	Staff Fellow	LB NIDR	Park, M.H.	Visiting Fellow	LB NIDR
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COOPERATING UNITS (if any) Dr. Jeffrey J. Gorman, University of Melbourne, Melbourne, Australia											
LAB/BRANCH Laboratory of Biochemistry											
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SUMMARY OF WORK (200 words or less - underline keywords) Studies on the specificity and catalytic mechanism of <u>transglutaminases</u> are underway. The relationships to <u>cellular control processes</u> and other physiological processes of <u>polyamine-protein conjugates</u> produced by these enzymes in both cells and body fluids are under investigation. Knowledge has been obtained concerning the <u>catabolism</u> of these amine-protein conjugates.											

1. Project Description

Objectives

Studies carried out over the past several years have been directed toward characterization of the transglutaminases and elucidation of their physiological functions. These enzymes catalyze post-translational modifications of proteins through the formation of γ -glutamyl amide bonds. The sites of enzymic attack are the carboxamide groups of glutamine residues. In the presence of acceptor amines, substituted amides are formed ($-\text{CONH}_2 + \text{RNH}_2 \rightarrow -\text{COHNR} + \text{NH}_3$).

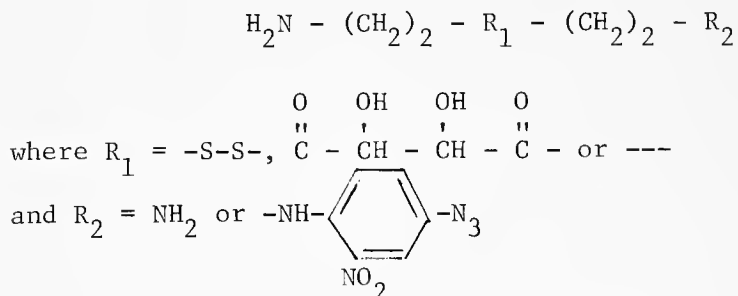
Among the products of transglutaminase action found in proteins of cell and body fluids are ϵ -(γ -glutamyl)lysine bonds, γ -glutamylputrescine, γ -glutamylpolyamines, γ -glutamylhistamine and bis(γ -glutamyl)polyamine bonds. There has been increasing evidence for the formation and importance of these transglutaminase products in fibrin clots, cell membranes, myofibrils of muscle, proteins of seminal plasma, wool keratin, citrulline-containing proteins of hair and numerous unidentified cellular proteins. The wide occurrence of transglutaminase products in biological systems, recent suggestions for involvement of transglutaminases in normal cellular processes, and our concern as to the mechanism by which the enzymic products are catabolized has led us to focus attention not only on the enzymes themselves, but on their biological roles. The means by which they express their cellular and extracellular functions, and the metabolism of transglutaminase-modified proteins promise to open new areas of interest.

This project is in part collaborative with S.I. Chung, Project #Z01 DE-00049-10 LB.

Major Findings

The specificities of the various transglutaminases are being systematically investigated. The basic model for these studies is a polypeptide fashioned after the region of β -casein which is most sensitive to the action of the enzymes. About 25 peptides containing variations in the sequence of amino acids surrounding glutamine 167 of β -casein have been prepared by means of solid phase synthesis. Preliminary tests show that several aliphatic hydrophobic amino acid residues on each side of the substrate glutamine are important for specificity of each of the enzymes. Although a lysine residue close to the glutamine is also a directive for specificity of blood coagulation factor XIIIa, chemical modification of this residue has been shown not to adversely effect specificity. These results, together with the findings with protein substrates, indicate that secondary enzyme-glutamine substrate interactions may, to a large extent, depend upon the tertiary structure of the substrate molecules. During the course of these studies several excellent low molecular weight substrates for factor XIIIa have been prepared.

A transglutaminase-mediated procedure for photochemical labeling of peptides and for production of cleavable crosslinks between molecules has been devised. Bifunctional amine substrates of the general structures:



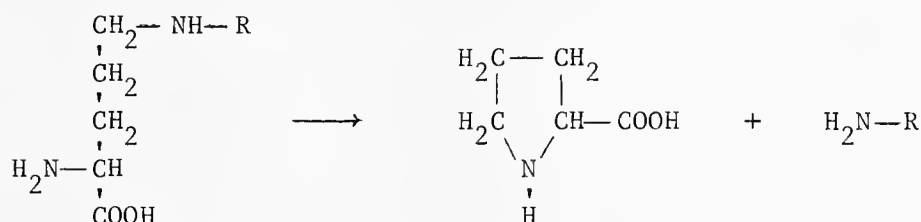
have been synthesized and employed to prepare photolabeled peptide hormones for receptor studies. To date, potentially useful photosensitive derivatives of substance P, glucagon 1-6, and human and salmon calcitonins have been prepared and fully characterized.

Catalytic mechanism studies conducted on factor XIIIa have revealed that this two-catalytic-subunit enzyme reacts with chemical active-site directed reagents in either a half-of-the-sites or an all-of-the-sites fashion, depending upon the conditions used. This finding supports an hypothesis of cooperativity, both positive and negative, between subunits and is apparently the first example of an enzyme in which a change from one type of cooperativity to another has been demonstrated.

Inactivation studies on the proenzyme forms of factor XIII in the presence of Ca^{2+} and on the enzyme, factor XIIIa, in the absence of the essential cation, Ca^{2+} , have supplied evidence for preformed catalytic sites within these molecules, as is the case with several pancreatic proteases and with blood coagulation factors VII and X. There is evidence from these studies that both proteolytic cleavage of activation peptide from zymogens and metal ion-induced conformational changes are essential to generate the glutamine substrate binding site within the enzyme.

Evidence has been accumulated that putrescine and the polyamines, spermidine and spermine, serve as physiological substrates for transglutaminases in both cells and body fluids. Crosslinks between proteins through polyamines occur in one extracellular system tested, clotting of rat seminal fluid. In human peripheral lymphocytes, although no evidence of crosslinking was obtained, protein conjugates of both putrescine and spermidine were found after treatment of cells with mitogens. In both systems the polyamines were found to be complexed through covalent γ -glutamyl linkage, strong evidence for their transglutaminase-catalyzed incorporation.

An enzyme that catalyzes the breakdown of ϵ -(γ -glutamyl)lysine, N-(γ -glutamyl)polyamines, N,N-bis-(γ -glutamyl)polyamines and a variety of other γ -glutamylamines has been found in numerous mammalian tissues and cell types. This enzyme, called γ -glutamylamine cyclotransferase, was first observed in and partially purified from rabbit kidney. It has been shown to catalyze the following reaction:



On the bases of preliminary studies of the products formed in cell lysates and intact cells, with and without inhibitors of proteolytic digestion and of the amine cyclotransferase, we propose that normal catabolism of ϵ -(γ -glutamyl)lysine crosslinked proteins and other transglutaminase-modified proteins proceeds with ultimate release of γ -glutamylamines, rather than by cleavage of γ -glutamyl bonds in the intact proteins. It appears that catalysis by γ -glutamylamine cyclotransferase is the essential last step in this process.

Significance

Knowledge of the molecular characteristics of the transglutaminases and of their catalytic mechanisms is vital to determination of the function of these enzymes in normal and diseased tissues, as well as to an understanding of the physiological and pharmacological control and regulation of their activity.

The minimal substrate structural requirements for transglutaminases have been defined over the past several years through studies such as those described. We now have a better understanding of the mechanisms of enzyme-substrate interactions in transglutaminase-catalyzed reactions. The techniques used for these studies, as well as ones used in determining specificity toward glutamine and lysine residues in macromolecular substrates, most certainly will show similarities, as well as differences, in the members of this important group of enzymes.

Amines, both polyamines and biogenic amines, and the transglutaminases are widely distributed. Both the amines and the enzymes may play important roles in control of growth and other biological processes. The finding that these amines are natural substrates for transglutaminases is an important first step in determining the role each plays in these vital processes. That there may be differences in the manner in which the amines serve as substrates in cells and in body fluids may contribute to our understanding of their possible function in control of cellular and extra-cellular processes.

Until now little has been known about the catabolism of products of transglutaminase action. The characterization and determination of the specificity of an enzyme, γ -glutamylamine cyclotransferase, that catalyzes breakdown of ϵ -(γ -glutamyl)lysine and other γ -glutamylamines is certainly vital in understanding the turnover of transglutaminase-modified proteins.

Proposed Course

The accumulated data on the specificity and catalytic mechanism of the transglutaminases indicate that the disposition of crosslinking and other modifications in substrate molecules is directed by secondary enzyme-substrate interactions and that these interactions are dependent to some degree upon substrate tertiary structure. The data also indicate that the stereospecificity of the enzymes is achieved by selective positioning of configurational isomers with respect to catalytic functionalities of the enzymes, rather than by preferential binding of L-residues. Proposals as to the specific manner by which the enzymes accomplish their catalytic goals have been made. Principle objectives will be to accumulate additional evidence in favor of these proposals, as well as to continue investigations of the role of multiple catalytic subunits and the importance of proteolytic modification and cation-induced conformational alterations in enzyme activation.

Attempts will be made to utilize the photosensitive hormone derivatives prepared by specific transglutaminase reactions to identify receptor molecules on cell surfaces. A search for other hormones amenable to this type modification and usage will be conducted.

Now that strong evidence has been obtained that the polyamines function as transglutaminase substrates, attempts will be made to determine how the products of these reactions participate in cellular and extracellular processes. First steps will involve characterization of the protein conjugates, identification of their cellular or extracellular location, and estimation of their metabolic rates and characteristics.

Knowledge of the specificity and distribution of the enzyme that breaks down γ -glutamyl derivatives should reveal much information about the basic catabolism of the products of transglutaminase action. For example, can crosslinks be hydrolyzed in intact proteins or must the proteins be largely degraded before the crosslinks can be cleaved? The answers to this and similar questions are of prime importance to a thorough understanding of the physiological role of these important enzymes.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00049-10 LB												
PERIOD COVERED October 1, 1980 to September 30, 1981														
TITLE OF PROJECT (80 characters or less) Physiological Role of Transglutaminases														
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Chung, S.I.	Research Chemist	LB	NIDR											
Chang, S.K.	Visiting Fellow	LB	NIDR											
Carmassi, F.	International Fellow	LB	NIDR											
COOPERATING UNITS (if any) Dr. Barbara Alving, WRMRI; Dr. J.S. Finlayson, FDA; Dr. Soo Young Lee, Catholic Medical School, Seoul, Korea														
LAB/BRANCH Biochemistry														
SECTION Enzyme Chemistry Section														
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, MD 20205														
TOTAL MANYEARS: <div style="text-align: right;">3.25</div>	PROFESSIONAL: <div style="text-align: right;">3.00</div>	OTHER: <div style="text-align: right;">.25</div>												
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) <p>The physiological function and the mode of regulation of the <u>transglutaminases</u> are being studied including their role in the modulation of specific cellular processes and in <u>fibrin-connective tissue</u> matrix stabilization during tissue repair. A novel form of transglutaminase, distributed in cell membranes and nucleus, has been isolated and characterized. This <u>membrane-associated transglutaminase</u>, which is present as an inactive form in resting cells, is one of the first enzymes to be activated during cell stimulation and proliferation.</p> <p>Physiological significance and biochemical mechanism of <u>Factor XIIIa</u> (plasma transglutaminase)-catalyzed crosslinking of fast-reacting plasmin inhibitor (α_2AP) to fibrin or other matrix proteins is under investigation both in vivo (Shwartzman's phenomenon) and in vitro. α_2AP crosslinked to fibrin has been shown to be resistant to plasminolysis.</p>														

1. Project Description

Objectives

The transglutaminases catalyze formation of covalent ϵ -(γ -glutamyl)lysine crosslinks within and between protein molecules. These bonds are of vital importance in blood coagulation, in seminal clot formation and in maintaining the structural integrity in certain hair, wool, and skin proteins. Furthermore, they may play an important role in wound healing and the modulation of membrane-mediated activation and proliferation of cells. The transglutaminases may also be involved in the modification of specific proteins by the introduction of biogenic amines.

The present objectives are: 1) to understand the mode of regulation of membrane-associated transglutaminase, isolation and characterization of intrinsic cellular substrate, and its cellular function. 2) to understand the physiological role of Factor XIIIa catalyzed crosslinking of α_2 AP, fibronectin, and α_2 macroglobulin to fibrin or other collagen tissue matrix in vivo (tissue repair and inflammation) and in vitro (cell adhesion or interaction with phagocytic cells).

Major Findings

1. Characterization and modulation of membrane-associated transglutaminase

Recently, cellular transglutaminases whose activities are modulated by various ligands have been reported. Chick-embryo epidermal cell transglutaminase is increased by hydrocortisone, peripheral blood lymphocyte enzyme by lectins, CHO cell enzyme by dibutyl cyclic AMP, and WI-38 cell and rabbit uterus epithelial cell enzyme by trypsin. However, these ligand-modulated cellular transglutaminases have neither been identified nor characterized.

From the detergent-extracted lysate of rat chondrosarcoma cells, two different molecular forms of the enzyme, which differ from previously characterized transglutaminases, have been isolated. Purification steps include ion-exchange and hydroxyapatite chromatography, gel-permeation and gel-electrophoresis. The amine-modified amino acids were identified as γ -glutamyl putrescine and γ -glutamyl spermine. This membrane-associated enzyme retains some of the characteristic properties of other transglutaminases, such as requirement for Ca^{2+} and sensitivity toward SH reagents. The distinct properties of this enzyme are: 1) Its molecular weight is estimated to be 100,000 but in the presence of a catalytic amount of thrombin, it converts to one-half of the original size along with a 4-fold enhancement of catalytic efficiency. 2) Substrate specificity is limited to a few proteins (casein and fibrin), and an effective dipeptide substrate, CBZ-GlnGly, for other intra-

cellular transglutaminases (liver or red blood cell) was neither substrate nor inhibitor.

In an effort to identify the intrinsic cellular substrate for this membrane-associated transglutaminase, whole cells or the isolated membrane fraction incubated with labeled putrescine or dansylcadaverine were analyzed for label incorporated proteins. An initial uptake of amine into low molecular weight protein (10,000) was peaked at 1 hr and decreased steadily. Labeling of a 230,000 molecular weight protein followed. The isolation and biochemical characterization of these labeled proteins are in progress.

Thrombin induces an activation of intracellular transglutaminase of rat chondrosarcoma cells in culture but without a decrease in molecular weight. Lysis of cells or an isolated membrane fraction showed no thrombin-induced activation of transglutaminase suggesting an indirect activation in whole cells. Studies done elsewhere are consistent in that cellular transglutaminase seems to be involved in receptor-mediated endocytosis since the inhibition of receptor endocytosis of α_2 macroglobulin and polypeptide hormones was correlated with the inhibition of intrinsic cellular transglutaminase by alkylamines and dansylcadaverine, known amine substrates for transglutaminase.

2. Physiological role of Factor XIIIa-catalyzed crosslinking of fibrin to other proteins.

We have shown that animals rendered deficient in plasma Factor XIII by administration of an equivalent titer dose of monospecific antibody to the zymogen display retarded wound healing. The platelet count and fibrinogen levels were unaffected by this treatment. Crosslinked clots formed in vitro are more resistant to fibrinolysis than if not crosslinked, but the relevance of these observations to the situation in vivo is uncertain. The possible role of Factor XIII in the formation of diffuse intravascular fibrin deposition was examined in these Factor XIII deficient rabbits by infusion of bacterial endotoxin. Histological examination of the kidney showed an extensive bilateral cortical necrosis in 8 of 10 control rabbits but none in the Factor XIII-deficient group. Fibrinolytic activity in vivo, studied by the degradation of infused [125 I]-labeled fibrinogen, was significantly increased in both groups, irrespective of Factor XIII levels. In addition, the crosslinked plasma clot is far more resistant than the Factor XIII-deficient plasma clot. The crosslinking of the fast-reacting plasmin inhibitor, antiplasmin (α_2 AP), to fibrin produces resistance to fibrinolysis. The physiological significance of clot stabilization, which may occur during inflammation and certain pathological conditions, prompted us to investigate the biochemical characterization of α_2 AP crosslinking to

fibrin and to other matrix proteins. The extremely labile α_2 AP was purified from plasma and monospecific antibody was prepared for future study. The lability of α_2 AP (loss of anti-plasmin activity) is concurrent with the autolytic fragmentation (65,000 to 50,000 and 15,000 molecular weight peptides). Intact, but not fragmented, α_2 AP was shown to be an effective substrate for Factor XIIIa.

Significance

The transglutaminases are ubiquitous enzymes involved in many biological processes. Except for fibrin crosslinking, very little is known about the mechanism or regulation of their various functions. The findings made so far, however, make it clear that a whole new area of biological investigation has been opened. The results will have important implications in stabilization of biological structure, in cell-matrix interactions (already shown in wound healing studies), and in several cellular processes.

Proposed Course

The mode of activation and of involvement of membrane-associated transglutaminase in such cellular processes as chemotaxis, receptor-mediated endocytosis, and membrane regeneration will be further investigated using a variety of cells. Attempts will be made to correlate the products of enzyme action with the cellular processes. Biochemical characterization and mechanism of α_2 AP and mode of crosslinking of antiplasmin to fibrin and matrix proteins are under investigation.

2. Publications

Gladner, Jules A., Lewis, Marc S., and Chung, Soo Il: Molecular properties of Lamprey fibrinogen. *J. Biol. Chem.* 256:1776-1781 (1981).

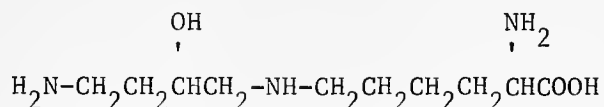
Fink, M. L., Chung, S. I., and Folk, J. E.: γ -Glutamine cyclotransferase: Specificity toward ϵ -(γ -glutamyl)-L-lysine and related compounds. *Proc. Natl. Acad. Sci.* 77:4564-4568 (1980).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00311-01 LB						
PERIOD COVERED October 1, 1980 - September 30, 1981								
TITLE OF PROJECT (80 characters or less) The Unusual Amino Acid, Hypusine: Mechanism of Formation and Function in Cellular Protein.								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 40%;">Folk, J. E.</td> <td style="width: 40%;">Chief, Enzyme Chemistry Section</td> <td style="width: 20%;">LB NIDR</td> </tr> <tr> <td>Park, M. H.</td> <td>Visiting Fellow</td> <td>LB NIDR</td> </tr> </table>			Folk, J. E.	Chief, Enzyme Chemistry Section	LB NIDR	Park, M. H.	Visiting Fellow	LB NIDR
Folk, J. E.	Chief, Enzyme Chemistry Section	LB NIDR						
Park, M. H.	Visiting Fellow	LB NIDR						
COOPERATING UNITS (if any) Dr. H.L. Cooper NCI, LPP								
LAB/BRANCH Laboratory of Biochemistry								
SECTION Enzyme Chemistry Section								
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, MD								
TOTAL MANYEARS: 1.25	PROFESSIONAL: 1.25	OTHER:						
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) <p>The <u>amino acid hypusine</u> has been identified in what appears to be the same single low molecular weight protein in numerous <u>mammalian cells</u>. Evidence has been accumulated for its <u>posttranslational</u> formation from lysine and the butylamine moiety of the <u>polyamine</u> spermidine, followed by hydroxylation. The findings demonstrate a novel polyamine <u>metabolic pathway</u>.</p>								

1. Project Description

Objectives

Studies carried out over the past year have served to identify hypusine



hypusine

as an amino acid component of what appears to be a single protein in all mammalian cells examined. In each cell type this component appears in a 18,000 molecular weight protein of $pI \sim 5.4$. Most interestingly, formation occurs only during the growth phase of the cells. The apparent ubiquity of this amino acid, its occurrence in a single protein in each cell type, and its unusual structure have led us to concentrate our attention on determination of its biological role and its mechanism of formation.

Major Findings

To date we have obtained experimental evidence that hypusine is formed during the growth of cells by a posttranslational mechanism in which the butylamine moiety of the polyamine, spermidine, is transferred to the ϵ -amino group of a protein-bound lysine residue. This rate limiting step in biosynthesis is followed by an oxidization step in which the intermediate, desoxyhypusine, is converted to the hydroxylated amino acid, hypusine.

In those cells examined, including various lymphocytes, fibroblasts, and epidermal cells, hypusine occurs in a single protein. Evidence that this protein is of low molecular weight has been obtained by exclusion chromatography of cell extracts. It appears to be primarily confined to the cytoplasmic portion of the cells. In resting cells no formation of hypusine can be observed. Formation occurs after about 10 hours following growth stimulation in lymphocytes.

Significance

The potential significance of what appears to be a rather elaborate limited posttranslational modification of a lysine residue (or lysine residues) in a single protein molecule in all mammalian cells seems obvious. At this time we have no clue as to the biological function of hypusine or of the hypusine-containing protein. We do, however, have evidence that a step involved in its biosynthesis constitutes a hitherto unrecognized pathway of polyamine metabolism. Further studies of the formation of this unusual amino acid and of its role in the cell should provide valuable new in-

formation both in the way of intermediate metabolism and structure-function relationships.

Proposed Course

The enzymic steps involved in posttranslational formation of hypusine are under study. Attempts will be made to identify the enzyme involved in hydroxylation of desoxyhypusine and to compare this enzyme with those that catalyze hydroxylation of proline and lysine in collagen and other proteins.

The use of ^{15}N - ϵ -labeled lysine should provide evidence as to whether a step in biosynthesis involves aldehyde formation and use of specifically labeled spermidine should supply clues to the mechanism of transfer of the butylamine moiety to lysine.

Attempts will be made to isolate and prepare antibody to the hypusine-containing protein. This should provide a first step in determining the biological role of this protein. Comparison of hypusine-containing proteins from various cells will be made by sequence analysis and peptide mapping. Data collected should prove the identity or show differences in the proteins from various cells.

2. Publications

Park, M.H., Cooper, H.L., and Folk, J.E.: Identification of hypusine, an unusual amino acid, in a protein from human lymphocytes and of spermidine as its biosynthetic precursor. Proc. Natl. Acad. Sci. USA 78:2869-2873, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00002-31 LB
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Structural Studies on Collagen		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between;"> Piez, K. A. Chief LB NIDR </div>		
COOPERATING UNITS (if any) Dr. Benes L. Trus, DCRT; Dr. Michael Beer, Johns Hopkins University; Dr. Joseph Wall, Brookhaven National Laboratory.		
LAB/BRANCH Laboratory of Biochemistry		
SECTION Protein Chemistry Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, MD 20205		
TOTAL MANYEARS: <div style="text-align: center;">1.75</div>	PROFESSIONAL: <div style="text-align: center;">.75</div>	OTHER: <div style="text-align: center;">1.00</div>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div> <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div> <div> <input type="checkbox"/> (b) HUMAN TISSUES </div> <div> <input checked="" type="checkbox"/> (c) NEITHER </div> </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <p> The primary goal of this project is an understanding of <u>collagen structure</u> from the molecular to the fibril level. Emphasis is presently on conventional and scanning transmission <u>electron microscopy</u> and analysis of micrographs to obtain quantitative data and reveal detail not obvious to the eye. Two types of specimen are being examined. One is negatively stained aggregates of collagen by conventional electron microscopy. The second is unstained aggregates of collagen by <u>scanning transmission electron microscopy</u>. Collaborative studies are also in progress using specifically heavy metal stained collagen samples by scanning transmission electron microscopy. The <u>image processing</u> techniques developed for this project have been shown to be generally applicable. </p>		

1. Project Description

Objectives:

The primary objective of this project is to determine the structure of the collagen molecule and of aggregates of collagen including the native collagen fibril. The major approaches are conventional electron microscopy (CEM) and scanning transmission electron microscopy (STEM). The results obtained will be correlated with data obtained by model building using the amino acid sequence and x-ray diffraction data. There is, for example, still not an agreed upon structure for the native collagen fibril.

Methods Employed:

For CEM, negatively stained specimens have been used. Procedures have been devised to obtain micrographs under minimal beam exposure to decrease radiation damage. STEM is being done in collaboration with scientists at Johns Hopkins using single-atom staining procedures and at Brookhaven using direct visualization of unstained specimens and mass measurements. Computer methods have been developed in collaboration with scientists in DCRT to process electron micrographs which are generally applicable to other images.

Major Findings:

Early aggregates formed during collagen assembly (see Z01 00215-05 LB) have been visualized both by CEM of negatively stained specimens and by STEM of unstained specimens. Under favorable conditions single collagen molecules can be seen. These aggregates are long thin structures containing many collagen molecules in a characteristic overlapping array. Preliminary results indicate that the overlap is about 50nm. This region is condensed while the region between, about 180nm, is spread out giving the appearance of nodes and internodes. The ratio of mass is about 2:1 in nodes:internodes. Since this structure does not appear to be related to the native fibril, it may not be a true intermediate but rather a byproduct.

Another approach to determining structure by STEM is to stain specific functional groups with single heavy atoms which can then be seen by STEM. From the known amino acid sequence, the staining pattern can be predicted. Preliminary experiments have been done in collaboration with scientists at Johns Hopkins on SLS aggregates of collagen and on single collagen molecules as control experiments. It has been possible to specifically stain methionine residues with a Pt reagent and carbohydrate residues with an Os reagent. Type III collagen can be distinguished from type I in model systems. These studies are being extended to tissue sections.

To resolve a conflict between a recently proposed model of the collagen fibril based on x-ray diffraction evidence and the microfibril model, supported by other data, we earlier proposed a revised model which contains "compressed" microfibrils placing molecules on a pseudohexagonal lattice. The unit cell provides an accurate fit of the observed reflections on the x-ray diffraction pattern and is consistent with other data. However, the molecular packing problem is still unresolved and is likely to remain so with this data alone.

Significance:

Collagen is the major protein of connective tissue and is found in various forms throughout the body. Through interactions with other macromolecules such as proteoglycans, mineral, and cells, it plays an important role in many biological processes during development and in pathological states. These studies on collagen structure are important to understanding these interactions.

Proposed Course:

Emphasis will continue to be placed on the development of procedures for specimen preparation of collagen aggregates, CEM and STEM of these aggregates and analysis of electron micrographs. There is some hope that with the right type of aggregate, the molecular packing problem can be solved. As this project progresses, collagen types other than type I and interactions of collagen with other components such as lysyl oxidase and proteoglycan will be studied by the same techniques. New techniques including rotary shadowing of molecules and small aggregates will be added.

Publications:

Piez, K. A.: Structure and function of collagen, in Gene Families of Collagen and other Proteins, (Prokop, D. J., and Champe, P. C., eds.) Elsevier/North Holland, New York, pp. 143-160 (1980).

Steven, A. C., Trus, B. L., Putz, C. and Wurtz, M.: The molecular organization of beet necrotic yellow vein virus. *Virology*. In press.

Trus, B.L., and Steven, A. C.: Digital image processing of electron micrographs. The PIC system. *Ultramicroscopy*. In press.

Nikodem, U. M., Trus, B. L., and Rall, J. E.: Two-dimensional gel analysis of rat liver nuclear proteins after thyroidectomy and thyroid treatment. *Proc. Nat. Acad. Sci.* In press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00157-06 LB												
PERIOD COVERED October 1, 1980 to September 30, 1981														
TITLE OF PROJECT (80 characters or less) Biophysical Studies on the Structure of Connective Tissue														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 50%;">Torchia, D. A.</td> <td style="width: 30%;">Biophysicist</td> <td style="width: 20%;">LB</td> <td style="width: 10%;">NIDR</td> </tr> <tr> <td>Batchelder, L. S.</td> <td>Staff Fellow</td> <td>LB</td> <td>NIDR</td> </tr> <tr> <td>Sarkar, S. K.</td> <td>Visiting Fellow</td> <td>LB</td> <td>NIDR</td> </tr> </table>			Torchia, D. A.	Biophysicist	LB	NIDR	Batchelder, L. S.	Staff Fellow	LB	NIDR	Sarkar, S. K.	Visiting Fellow	LB	NIDR
Torchia, D. A.	Biophysicist	LB	NIDR											
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COOPERATING UNITS (if any) Dr. A. N. Schechter, NIAMDD														
LAB/BRANCH Laboratory of Biochemistry														
SECTION Protein Chemistry Section														
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, MD 20205														
TOTAL MANYEARS: <div style="text-align: right;">4.50</div>	PROFESSIONAL: <div style="text-align: right;">2.50</div>	OTHER: <div style="text-align: right;">2.00</div>												
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) <p> The purpose of this project is to investigate the molecular structure of fibrous proteins and proteoglycans, and to study intracellular gelation of Hemoglobin S. The structural information obtained will be correlated with function. Areas of present interest are 1) <u>Molecular structure and dynamics of collagen</u>. ¹³C and ²H magnetic resonance techniques are being used to study the structure and interactions in collagen fibers. 2) <u>Proteoglycan structure</u>. ¹³C magnetic resonance is also being used to study the molecular mobility of the polysaccharide and protein chains in cartilage proteoglycans. 3) ¹³C magnetic resonance is being used to study the extent and mechanism of <u>hemoglobin S gelation</u> in erythrocytes. For these studies, magnetic resonance spectrometers have been assembled which give ²H, ¹³C and ³¹P spectra of solids. High power decoupling, cross-polarization, magic angle spinning, and solid echo experiments are all performed. </p>														

Introduction

The goal of this work is to determine aspects of the molecular structure and interactions of macromolecules in connective tissue and to elucidate structure-function relationships. In addition, a collaborative study on hemoglobin S has been undertaken since our methods are unique at NIH and the problem is important.

Methods

The primary research tool employed is nuclear magnetic resonance (nmr). Until recently, high resolution nmr studies had been limited to flexible macromolecules since linewidths of rigid structures having high molecular weights were too broad to detect. However, structured molecules can now be studied in the solid state by decoupling the dipolar interactions between proton and ^{13}C or ^{31}P nuclei. Cross-polarization is used to enhance ^{13}C or ^{31}P signals in rigid molecular lattices where long spin-lattice relaxation times make normal Fourier transform techniques impractical. In addition, cross-polarization can be combined with rapid spinning of the sample about the magic axis (an axis making an angle of 54.7° with the external magnetic field) to produce spectra having small linewidths, comparable to those obtained for samples in solution. In the case of ^2H nuclei, decoupling is not required and spectra can be measured directly using a solid echo technique.

We have built two pulsed nmr spectrometers which provide solid state spectra of ^2H , ^{13}C and ^{31}P . High resolution cross-polarization spectra and normal Fourier transform spectra (of ^{13}C and ^{31}P) can be routinely obtained for samples ranging from inorganic crystals to whole tissues, and magic angle spinning spectra can be obtained for ^{31}P . Relaxation times in the laboratory and rotating frames, cross-polarization times, and chemical shift anisotropies can all be measured and provide information about molecular orientation and molecular motions covering the frequency range 10^3 to 10^{10} Hz. Deuterium quadrupole coupling constants and lineshapes are obtained from ^2H spectra and are sensitive to molecular motions in 10^4 - 10^6 Hz frequency range.

Unlike ^{31}P , the natural abundances of ^2H and ^{13}C are low (0.016 and 1.1%, respectively). Hence, it is advantageous to incorporate labeled amino acids into proteins under study. The presence of the label greatly simplifies interpretation of the spectra since the ^2H and ^{13}C resonances can readily be assigned to the labeled sites. We have used biosynthetic techniques to incorporate ^2H and ^{13}C labeled amino acids into collagen and proteoglycans.

Progress

1. Molecular Structure and Dynamics of Collagen.

Spectra of chick calvaria collagen fibrils containing a ^{13}C or ^2H labeled amino acid have provided strong evidence that rapid, anisotropic molecular motion occurs in the helix backbone and in the labeled sidechains.

In our recent work we have analyzed ^2H nmr lineshapes to derive specific models of the motion of collagen sidechains in fibrils. X-ray studies of peptides and proteins containing leucine have shown that the leucine sidechain assumes one of two low energy conformations in crystals. We have found that in collagen fibrils, the leucine sidechains "hops" between these two conformations with a rate that increases from 10^3 to 10^6 s^{-1} as the temperature increases from -89° to $+30^\circ\text{C}$. In addition, although the flexibility of the proline sidechain is constrained by the pyrrolidine ring, our ^2H spectra of collagen fibrils show that the β and γ positions of the ring are significantly more flexible than the α position.

The backbone and sidechain flexibility of collagen fibrils is markedly reduced if the fibrils are dried or frozen, a result that implies that mobile water is responsible for collagen fluidity. This conclusion has been confirmed by ^{13}C nmr spectra of mature bovine tibia which has a very low water content and shows a significant reduction in collagen flexibility.

2. Proteoglycan Dynamics and Structure.

Our recent nmr studies have shown that at least 75% of glycosaminoglycan and protein chains in cartilage proteoglycans exhibit segmental flexibility similar to unordered polymer chains. Solution studies have shown that glycosaminoglycan chain flexibility decreases with increasing concentration and we are currently examining the effect of compression (and concomitant water loss) upon the mobility of glycosaminoglycan chains in intact bovine nasal cartilage. This is in collaboration with Dr. V.C. Hascall, Project # Z01 DE-00134-07 LB.

3. ^{13}C nmr of Hemoglobin S Gelation

We have shown that ^{13}C nmr is a reliable means of quantitating the amount of polymer in cell-free deoxygenated hemoglobin S gels and within intact red cells. The nmr spectra have shown that the amount of polymer in SS Erythrocytes decreases with increasing oxygen saturation but that approximately 10% polymer remains at oxygen saturation values above 95%. In contrast, SA red cells have insignificant amounts of polymer when oxygen saturation exceeds 60%. Although theoretical considerations suggest that these results can be in part accounted for by excluded volume effects, it is also possible that the presence of irreversibly sickled cells in the heterogeneous SS cell population is responsible.

Our current work focuses upon examining cell populations that have been fractionated according to hemoglobin concentration to investigate this point.

Significance

Interactions involving specifically labeled sites have been investigated using the new experimental technique of high resolution nmr in solids in conjunction with ^2H and ^{13}C labeled tissues. New information about the molecular dynamics and interactions at specific sites in intact connective tissue has been obtained. This information has provided a basis for understanding the nature of the molecular interactions that determine the structure and function of the macromolecules investigated. In addition, ^{13}C nmr is a useful method for investigating the mechanism of gelation within intact red cells and the activity of potential inhibitors.

Future Plans

The general strategy of using solid state and solution nmr to study labeled macromolecules will be followed. Emphasis will be placed upon studies using the high field nmr spectrometers that have recently become available at the NIH. In particular we will investigate 1) the structure of the non-helical regions of collagen at various stages during fibril formation; 2) the thermal unfolding of the triple helix in solution and in intact tissue; 3) the cis-trans isomerization of the X-Pro peptide bonds in denatured collagen; 4) the effect of compression on the mobility of glycosaminoglycan chains in cartilage; 5) the effect of the intracellular hemoglobin S concentration on polymer formation in red cells.

Publications

L.W. Jelinski, C.E. Sullivan, and D.A. Torchia: Effect of proton spin diffusion on the ^{13}C -(^1H) NOE in hydrated macromolecules. J. Mag. Res. 41, 133-139 (1980).

C.T. Noguchi, D.A. Torchia and A.N. Schechter: Determination of deoxy-hemoglobin S polymer in sickle erythrocytes upon deoxygenation. Proc. Natl. Acad. Sci. 77;5487-5491 (1980).

L.W. Jelinski, C.E. Sullivan, L.S. Batchelder and D.A. Torchia: Deuterium nuclear magnetic resonance of specifically labeled native collagen. Investigation of protein molecular dynamics using the quadropolar echo technique. Biophys. J. 41;133-139 (1980).

L.W. Jelinski and D.A. Torchia: High power proton decoupled ^{13}C NMR study of molecular motion in specifically labeled collagen. Frontiers in Protein Chemistry, (Liu, D.H., ed.) Elsevier North Holland Inc. pp. 89-115 (1980).

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D.A. Torchia: Solid state NMR studies of collagen fibrils. in Methods in Enzymology, Structural and Contractile Proteins, (Cunningham, L.W. and Frederiksen, D.F., eds.) In press.

D.A. Torchia, L.S. Batchelder, L.W. Jelinski and C.E. Sullivan: Molecular dynamics of ^2H labeled amino acid residues in collagen fibrils. Polymer Reprints. In press.

C. T. Noguchi, D. A. Torchia, and A. N. Schechter: Polymerization of hemoglobin in sickle trait erythrocytes and lysates. J. Biol. Chem. 256:4168-4171 (1981).

C. T. Noguchi, A. N. Schechter, D. A. Torchia: The effect of oxygen saturation on the intracellular polymerization of sickle hemoglobin. Interactions Between Iron and Proteins in Oxygen and Electron Transport. (Ho, C., ed.) Elsevier/North Holland Inc. In press.

C. T. Noguchi, D. A. Torchia, and A. N. Schechter: Determination of sickle hemoglobin polymer in SS and AS erythrocytes. Blood Cells. In press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00215-05 LB						
PERIOD COVERED <p style="text-align: center;">October 1, 1980 to September 30, 1981</p>								
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">Connective Tissue: Formation and Structure</p>								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Lee, S. L.</td> <td style="width: 33%;">Staff Fellow</td> <td style="width: 33%;">LB NIDR</td> </tr> <tr> <td>Piez, K.A.</td> <td>Chief</td> <td>LB NIDR</td> </tr> </table>			Lee, S. L.	Staff Fellow	LB NIDR	Piez, K.A.	Chief	LB NIDR
Lee, S. L.	Staff Fellow	LB NIDR						
Piez, K.A.	Chief	LB NIDR						
COOPERATING UNITS (if any) <p style="text-align: center;">None</p>								
LAB/BRANCH <p style="text-align: center;">Laboratory of Biochemistry</p>								
SECTION <p style="text-align: center;">Protein Chemistry Section</p>								
INSTITUTE AND LOCATION <p style="text-align: center;">NIDR, NIH, Bethesda, MD 20205</p>								
TOTAL MANYEARS: <p style="text-align: center;">2.00</p>	PROFESSIONAL: <p style="text-align: center;">1.25</p>	OTHER: <p style="text-align: center;">.75</p>						
CHECK APPROPRIATE BOX(ES) <table style="width: 100%; border: none;"> <tr> <td><input type="checkbox"/> (a) HUMAN SUBJECTS</td> <td><input type="checkbox"/> (b) HUMAN TISSUES</td> <td><input checked="" type="checkbox"/> (c) NEITHER</td> </tr> <tr> <td><input type="checkbox"/> (a1) MINORS</td> <td><input type="checkbox"/> (a2) INTERVIEWS</td> <td></td> </tr> </table>			<input type="checkbox"/> (a) HUMAN SUBJECTS	<input type="checkbox"/> (b) HUMAN TISSUES	<input checked="" type="checkbox"/> (c) NEITHER	<input type="checkbox"/> (a1) MINORS	<input type="checkbox"/> (a2) INTERVIEWS	
<input type="checkbox"/> (a) HUMAN SUBJECTS	<input type="checkbox"/> (b) HUMAN TISSUES	<input checked="" type="checkbox"/> (c) NEITHER						
<input type="checkbox"/> (a1) MINORS	<input type="checkbox"/> (a2) INTERVIEWS							
SUMMARY OF WORK (200 words or less - underline keywords) <p> It is the long range purpose of this project to study interactions and relationships between <u>connective tissue</u> macromolecules as a way to understand connective tissue formation and structure. The topics of present interest are: 1) The mechanism of <u>collagen fibril formation in vitro</u>. 2) The effect of noncollagenous molecules on collagen assembly <u>in vitro</u>. We have developed a reproducible <u>in vitro</u> assembly system and shown that <u>Type I collagen</u> from rat tail tendon assembles in a multistep process. Studies are being extended to <u>lathyrctic Type I collagen</u> from rat skin and <u>type II collagen</u> from rat chondrosarcoma. </p>								

Project DescriptionObjectives

1. The mechanism of collagen fibril formation in vitro.

The development of a well-characterized, reproducible system for the study of collagen fibril formation in vitro and of models of fibril structure has made it possible to investigate the mechanism of collagen assembly in greater detail than previously possible. Studies on the structure of early aggregates are now part of project Z01 DE-00002-31 LB. Earlier studies utilized normal type I collagen from rat tail tendon. Lathyrctic type I collagen from rat skin and type II collagen from rat chondrosarcoma are also now being used.

2. The role of noncollagenous molecules in collagen assembly and fibril structure.

In vivo, collagen assembles in the presence of a variety of macromolecules and low molecular weight substances. Although none of these (except perhaps phosphate) appears to be necessary for in vitro assembly, it is likely that they may be involved in vivo, perhaps to regulate the process. Of particular interest are proteoglycan, lysyl oxidase and fibronectin. Preliminary experiments are being done to study proteoglycan and lysyl oxidase.

Methods Employed

Normal type I collagen is prepared from rat tail tendon, and purified and characterized by standard biochemical and biophysical methods. Lathyrctic type I collagen is being prepared from rat skin and type II from rat chondrosarcoma. Fibril structure and kinetics of formation are being studied by electron microscopy, turbidity and chemical determination of crosslink location.

Progress

1. The mechanism of collagen fibril formation.

A set of optimal conditions for the self-assembly process in vitro has been selected and used in an investigation of the mechanism of collagen assembly. We have reported that our observations of normal type I collagen assembly suggest a mechanism of at least three steps. Step 1, initiation, involves a temperature-dependent change which leads to an intermediate aggregate. Step 2 is linear growth of thin filaments by a temperature-independent process. The mechanism of growth is not known but may require a reorganization of molecules. Step 3 is lateral association of filaments by a temperature-dependent process. The concentration dependence of the rates of Steps 2 and 3, and the lack of a measurable critical concentration suggest assembly by accretion rather than classical nucleation. Collagen treated with pepsin, which removes the nonhelical

ends, makes distorted fibrils by a similar mechanism. However, assembly is very much slower and Step 1 is markedly altered. The nonhelical ends therefore are critically involved in assembly.

Studies with lathyritic type I collagen and type II collagen (also lathyritic) suggest that the multistep model may be oversimplified. For example, the rate of assembly of these lathyritic collagens is much slower. Since the major difference is that these collagens are lathyritic and do not crosslink, crosslinking may affect the kinetics by driving the reaction to completion. A reassessment of the mechanism is underway.

2. Size and structure of early intermediates in assembly.

Quasielastic light scattering has shown that an aggregate <8 nm in diameter and >1500 nm long is an early aggregate and a product of Step 1. An aggregate satisfying these requirements has been seen by both conventional electron microscopy and by scanning transmission electron microscopy (see project Z01 DE-00002-31 LB). Preliminary determinations of its structure raise the possibility that it is not a true intermediate but a byproduct.

3. The effect of proteoglycan on collagen assembly in vitro.

Preliminary studies on the effect of lysyl oxidase on assembly of lathyritic collagen and of proteoglycan on type II collagen are underway. It is still too early to assess results.

Significance

The basic properties of connective tissues can be described in terms of the macromolecules of which they are composed. Of these, collagen is the major structural protein. Collagen is present as native fibrils which vary in diameter and in their higher level organization as a function of species, tissue and developmental stage. In some tissues, such as cartilage, proteoglycan is also a major component. Lysyl oxidase is always present since it forms aldehydes in collagen prior to crosslinking. Information regarding the mechanism of assembly and interactions with other macromolecules provides a basis for continued research on tissue development and on the relationship of structure to disease.

Proposed Course

Our studies will emphasize the mechanism of in vitro assembly of collagen using lathyritic collagen and type II collagen. When these systems are understood, we will investigate the role of other macromolecules in the process, particularly proteoglycan and lysyl oxidase.

Publications

Gelman, R. A., and Piez, K. A.: Collagen fibril formation In Vitro. A quasielastic light scattering study of early stages. J. Biol. Chem. 255: 8098-8102, 1980.

Piez, K. A., Gelman, R. A., Williams, B. R., and Poppke, D. C.: Assembly of collagen In Vitro. Proceedings of the Seventh Aharon Katzir-Katchalsky Conference. In press.

Piez, K. A.: Structure and assembly of the native collagen fibril. Proceedings of the International Symposium on Connective Tissue Matrix Molecules. In press.

Summary Statement
Laboratory of Microbiology and Immunology
National Institute of Dental Research

The major research programs of the Laboratory of Microbiology and Immunology continue to focus on the oral microbial flora and on the immunological responses of the host. However, with the departure of two key staff members, Drs. Steven Mizel and Donald LeBlanc, during the past year the continuity and subsequent progress in major research components of the laboratory were seriously affected. More specifically, Dr. LeBlanc was one of the outstanding and highly effective leaders in our plasmid biology program while Dr. Mizel was instrumental in bringing biochemical expertise to our newly emerging research on the isolation and purification of hormone-like mediators from lymphocytes and macrophages. Our present concern is to recruit scientists with comparable backgrounds in order to pursue research in these important areas. The following is a summary of our progress during the past year as reported by the individual Sections.

The Microbiology Section reported previously on a highly specific form of cell-cell recognition between certain species of Actinomyces and Streptococcus sanguis that resulted in the formation of large macroscopic aggregates. These interactions (coaggregations) appear to be mediated by complementary surface components composed of a lectin on one cell type and a carbohydrate receptor on the other cell type. Intergeneric coaggregations are important in plaque development and our ecology program continues to focus on their distribution among oral bacteria as well as on attempts to characterize the cell surface structures involved.

Previously described coaggregations were confined to species of Actinomyces and strains of S. sanguis. We now report that coaggregation also occurs between strains of A. israeli and various species of Cytophaga and Capnocytophaga. Some of these interactions are lactose reversible, while others are not. Thus, coaggregation appears to be a widespread phenomenon among the oral bacterial flora, although the cell surface structures involved are different.

The coaggregations that occur between oral actinomycetes and streptococci are limited to five kinds. Each kind is mediated by a single pair of complementary surface components. However, the participating cells possess other surface components that are involved in other kinds of coaggregations. In an effort to gain insight into the precise nature of these surface components, a selection technique has been developed to isolate spontaneously occurring coaggregation defective mutants. A collection of such mutants has now been obtained and they are being used to analyze independently each surface component involved in each kind of coaggregation. This aspect of our study is being done in collaboration with the Humoral Immunity Section.

The Section has continued its inquiries into the mechanisms by which carbohydrates and pentitols are transported and metabolized by the lactic acid bacteria. Emphasis has been placed on the development and utilization of genetic approaches and molecular biological techniques in these studies.

Streptococcus mutans transports most fermentable carbohydrates by means of a phosphoenolpyruvate phosphotransferase system (PTS). Using mutants defective in the glucose PTS, it has been possible to demonstrate that this organism possesses a second, non-PTS transport system for glucose. This second transport system has recently been found to involve a proton motive force driven permease.

Genes that code for lactose utilization are located on the chromosome in S. mutans and S. sanguis, but are carried on a plasmid in Streptococcus lactis. The lactose genes have been used as a model for developing a genetic exchange system that can be used with many species of streptococci. Mutants that were missing either lactose PTS or phospho- β -galactosidase or both were constructed from a strain of S. sanguis that is competent for heterologous DNA transformation. Purified S. mutans DNA and S. lactis plasmid DNA are capable of repairing both lactose genetic lesions when introduced into the recipient S. sanguis mutant. Analysis of the transformants has revealed that both the lactose PTS and phospho- β -galactosidase genes are transferred from the S. lactis plasmid into the chromosome of S. sanguis and transformation frequency studies demonstrated that the genes are linked.

We reported previously on the presence of several plasmids in strains of L. casei, although no function could be ascribed to them. The development of a system for the conjugal transfer of plasmids among strains of L. casei has been an important breakthrough for further examination of this problem.

Using this system, evidence was obtained which strongly suggested that one of the plasmids carried genes for lactose utilization as was found for S. lactis. These results have recently been confirmed by the molecular cloning of L. casei plasmid DNA into Escherichia coli. Recombinant clones expressing phospho- β -galactosidase activity were shown to contain a 7.1 KBp insert of L. casei plasmid DNA in the PST I site of pBr322.

Our studies on pentitol metabolism by lactic acid bacteria continue. A group of L. casei and S. avium mutants blocked at each step of transport and catabolism are being used to delineate the pathways involved in the dissimilation of these unusual growth substrates. Thus far a membrane-bound enzyme II and a soluble enzyme III component of the xylitol PTS system have been extensively purified and partially characterized. In addition one of the catabolic enzymes, xylitol-5-P dehydrogenase has been partially purified. Interestingly, this enzyme also exhibits D-arabitol-5-P dehydrogenase activity. These studies continue to advance our knowledge about the metabolic diversity of the oral microbial flora and contribute to our better understanding of the complex oral ecosystem.

Plasmids and their role in the physiology and ecology of the oral streptococci represents another area under investigation. A strain of S. mutans isolated from the jaw of a pig that was maintained on tetracycline supplemented feed was shown to be resistant to four antibiotics; erythromycin, lincomycin, tetracycline and streptomycin. Resistance to both erythromycin and lincomycin is typically due to a plasmid, but it has not been possible to detect a plasmid in this strain of S. mutans.

It has been possible, however, to demonstrate the transfer of tetracycline resistance from the porcine strain to human isolates of S. faecalis and S. mutans by a conjugation-like process. Moreover, the tetracycline resistant transconjugates have been found to contain an 8 Mdal plasmid. Since the porcine donor strain did not contain a plasmid, a current working hypothesis is that tetracycline resistance is encoded on the chromosome, but that it is able to excise, transfer, and replicate independently in the transconjugants.

The Cellular Immunology Section is investigating basic mechanisms by which host defenses to microbial and other antigens mobilize and modulate cellular and antibody mediated inflammatory reactions. A major effort involves the study of hormone-like immunoregulatory factors produced by inflammatory cells. Both the biological effects and biochemical characteristics of a number of these mediators are being intensively investigated. These mediators which are produced by stimulated monocytes, lymphocytes, growing keratinocytes or cell lines are produced in small amounts and are active at 10^{-10} to 10^{-15} M concentrations which complicates their biochemical purification.

The mediators being investigated by members of the section include mouse colony stimulating factor (CSF), mouse and human interleukin 1 and 2 (IL 1 and 2), mouse immune interferon (IF) and human macrophage activating factor (MAF). During the past year, members of the section were successful in separating CSF from the other activities produced by mouse splenic lymphocytes and cell lines, and developed methodology for producing CSF in quantity by cell lines which will facilitate further progress in its purification.

Macrophage derived IL 1 has been shown to enhance not only the functions of Lyt 1 types of helper lymphocytes, but also hepatocyte production of acute phase proteins, fibroblast growth and prostaglandin production and to stimulate hypothalamic cells which results in fever. A similar biological activity called ETAF has been found to be produced by epidermal keratinocytes which suggests that upon injury skin cells can produce a mediator that promotes local as well as systemic inflammatory and reparative responses. IL 1 and ETAF are both being purified and production of monoclonal antibodies against these activities is underway.

IL 2 is produced in sufficient amounts by mouse and human lymphocyte lines to enable purification and recovery of visible bands from polyacrylamide gel electrophoresis. Sufficient partially purified human IL 2 was obtained to immunize mice and prepare, in collaboration with the Clinical Immunology Section, hybridoma derived monoclonal antibodies. The anti-IL 2 inhibits the T cell growth factor activity of IL 2, in vitro lymphoproliferative responses to lectins and antibody production in response to antigens as well as to polyclonal B cell mitogens. The capacity of the antibody to block virtually all in vitro immunological responses emphasizes the central role of this amplifying signal in immune responses. These antibodies can also be used to develop radioimmunoassays, immunoaffinity columns and for gene cloning studies involving IL 2.

It has been observed that macrophage expression of Ia antigens is associated with the capacity of such cells to induce immune responses, whereas Ia negative macrophages fail to do so. However, Ia negative macrophages can be converted into Ia positive cells by a lymphokine. The lymphokine responsible for this differentiating effect has been identified as immune interferon. This Ia-inducing activity may account for the in vivo immunoenhancing effects that have been attributed to interferon. In addition, macrophages are activated to produce H_2O_2 by another lymphokine which is presumed to be MAF. A quantitative and easy assay for H_2O_2 detection has been developed. Human cell lines that produce "MAF" activity and others that produce H_2O_2 in response to "MAF" have also been identified. This will enable us to isolate and characterize the lymphocyte derived H_2O_2 inducing factor. Other studies have revealed that neutrophils and activated macrophages produce oxygen intermediates including H_2O_2 as well as prostaglandins which have inhibitory effects on immunological reactions, but also can participate in tumor cell and bacterial killing by macrophages. The capacity of neutrophils and macrophages present in gingival fluid of normal subjects to phagocytize and produce oxygen intermediates has been established and will be compared to cells obtained from patients with periodontal diseases.

As an indication of the relevance of the aforementioned studies, investigators in the Cellular Immunology Section have received more invitations to national and international meetings, and to contribute chapters to books than they can handle. In addition, they are supplying many other investigators in the USA, Europe and Asia on request with cell lines, partially purified mediators and monoclonal antibodies that are needed to pursue their experimental studies.

A major area of emphasis of the Humoral Immunity Section continues to be the investigation of the immunological regulation of connective tissue destruction, repair and hypertrophy. These opposing processes are, at least partially, controlled by products of immunologically competent cells. Thus, activated macrophages produce factors which not only degrade collagen (collagenase) but, in addition, initiate the directed migration of fibroblasts as well as the proliferation of and collagen synthesis by these cells. Activated lymphocyte products also directly influence connective tissue metabolism by stimulating fibroblast proliferation and collagen synthesis and indirectly by secreting factors which, in turn, induce the production of the previously mentioned macrophage derived mediators. Characterization of the macrophage products reveals that the directed migration of fibroblasts is initiated by a monokine distinct from that which stimulates the proliferation of and collagen synthesis by these cells. The chemotactic factor has been identified as fibronectin and its production, like that of collagenase, requires prior prostaglandin synthesis.

Attempts to correlate some of these in vitro findings with in vivo pathological alterations of connective tissue metabolism have been initiated. The appearance of polyarthritis in susceptible rats injected with group A streptococcal cell wall preparations is preceded by severe immunosuppression. Those animals which develop arthritis recover immune functions such as lymphocyte proliferation and lymphokine production more rapidly than rats which are resistant to this disease process.

Thus, the development of arthritis is associated with the return of some functions of the immune system. Of interest is the finding that the macrophages from resistant animals which received the cell wall preparations synthesize greater levels of prostaglandin E₂ than do those from susceptible rats. These prostaglandins may contribute to the immunological suppression observed in the resistant animals. The elevated levels of prostaglandins also indicate the occurrence of in vivo macrophage activation; a process which would favor clearance of the arthritis-inducing agent.

In a clinical situation, lymphophoresis has been effective in the treatment of some rheumatoid arthritis patients. Evaluation of the immune status of a group of these patients prior to and during repeated lymphophoresis therapy has provided a fairly reliable means of predicting which patients will benefit from this treatment. The majority of those patients which exhibit severe immunosuppression of lymphocyte proliferation respond to treatment whereas those with normal proliferative responses do not. As lymphophoresis of the severely immunosuppressed patients proceeds, lymphocyte function is restored, indicating that removal of an as yet unidentified population of suppressor cells can alleviate symptoms in some arthritis patients.

Abnormalities of the immune system are also associated with defective bone resorption. Studies concerning osteopetrosis, a disease which can be cured by syngeneic spleen or bone marrow transplantation, have clearly demonstrated that although defects are present in both lymphocytes and macrophages from osteopetrotic (op) rats, these cells do possess some normal functions. Whereas the mitogen induced proliferative response of lymphocytes from affected animals is suppressed, their production of a lymphocyte derived chemotactic factor is not. Similarly, macrophages from op rats produce normal levels of prostaglandin E₂ following activation, but their response to chemotactic factors and their production of a monokine which is chemotactic for fibroblasts is impaired. Thus, it is becoming apparent that more than one cell population may be defective in osteopetrotic animals and that the abnormalities are not associated with total immunological dysfunction of a particular cell type.

Another major area of emphasis of this section is the definition of the mechanisms by which oral microorganisms adhere to other microorganisms and mammalian cells. Immunochemical techniques, particularly those utilizing monoclonal antibodies, have been employed to purify and characterize fibrillar structures present on the surface of Actinomyces viscosus T14V. One of these (Ag2) has been shown to possess a lectin which mediates lactose-inhibitable coaggregation with other bacteria and neuraminidase treated erythrocytes. The second fibrillar component (Ag1) lacks this lectin activity but may contribute to one or more of the previously described adherence reactions in which A. viscosus T14V participates. Recently, in collaboration with the Microbiology Section, mutants of A. viscosus T14V, which are specifically defective in lactose-inhibitable adherence, were shown to completely lack immunochemically detectable Ag2 but to possess Ag1. Attempts to localize the lectin activity on Ag2 fibrils have been initiated. Fab fragments of Ag2 specific rabbit antibodies block lactose inhibitable adherence of A. viscosus T14V. Interestingly, although all the monoclonal antibodies produced against this antigen inhibit adherence, their Fab fragments lack this activity. Thus, these fragments may not be reacting with or in close proximity to the lectin combining sites on the fibrils. Alternatively, more than one site on the fibril may be involved in lactose inhibitable

coaggregation. Since adherence is the critical event in many bacterial infections, precise identification of the surface structures involved may provide rational approaches to the development of specific therapeutic agents.

Host defense against tumors might be augmented by enhancing the migration of macrophages into a tumor site. A macrophage chemotactic response localized in a tumor has been produced by the injection of guinea pigs bearing intraperitoneal hepatomas with anti-hepatoma antibodies covalently coupled to the synthetic chemoattractant, formyl-methionyl-leucyl-phenylalanine (fMLP). These antibody-fMLP complexes were previously shown to possess chemotactic activity *in vitro* and to bind to surface antigens on tumor cells. The numbers of macrophages infiltrating both the peripheral and central areas of the tumors were significantly greater in animals injected with antibody-fMLP than in those which received phosphate buffered saline, antibody or free fMLP. The mean tumor weights of the groups of animals injected with antibody-fMLP were lower than those which received the other reagents but these differences were not statistically significant due to marked individual variation. Thus, antibody-chemotactic factor complexes may provide a novel approach to the therapeutic management of some malignancies by enhancing the influx of macrophages into tumors, a response which is known to favor tumor destruction.

The Clinical Immunology Section is continuing studies on the mechanisms of cell secretion. A rat basophilic leukemia cell line has been developed which has cell surface immunoglobulin receptors and can be triggered to release its cellular content of histamine and serotonin. These cells have been used to study the biochemical events which accompany exocytosis. The stimulation of cell surface immunoglobulin receptors causes a transient increase in phospholipid methylation, Ca^{2+} influx and the release of arachidonic acid. The release of arachidonic acid is due to the activation of phospholipase which is an essential step in the histamine release pathway. The arachidonic acid is metabolized further mainly by the cyclooxygenase pathway to prostaglandin D_2 . The inhibition of the further metabolism of arachidonic acid does not affect histamine release. These findings strongly suggest that immunoglobulin receptors, phospholipid methyltransferase enzymes, Ca^{2+} ion channels and phospholipase are clearly associated in the cell surface.

The isolation of variants of the rat basophilic leukemia cell line has made it possible to further analyze the histamine secretory pathway. A number of variants have been identified which have defects at different stages in the histamine release process. This allows us to determine sequence of biochemical steps. Thus it can be shown that cell surface receptor aggregation is followed by methylation, Ca^{2+} influx, arachidonic acid and histamine release. However, there are other variants with defects in intermediate steps in the pathway e.g. increased phospholipid methylation not followed by Ca^{2+} influx or arachidonic acid release not followed by histamine release.

The methylation of membrane phospholipids is an important event preceeding histamine release. Phospholipid methyltransferase enzymes are present in a number of tissues. The first enzyme, phospholipid methyltransferase I (PMT I) faces the intracellular compartment and transfers one methyl

group from S-adenosylmethionine to phosphatidylethanolamine to produce mono-methylethanolamine. The second enzyme, phospholipid methyltransferase II (PMT II) adds two more methyl groups resulting in the final formation of phosphatidylcholine. It has been suggested that these phospholipid methyltransferases function in signal transduction across the cell membrane in a variety of different systems. Fifty drug resistant variants of the rat basophilic leukemia cells were tested to find cell lines which were defective for these two phospholipid methyltransferase enzymes (PMT I and II). Two cell lines were recognized which have decreased levels of the two enzymes and do not release histamine to an IgE- stimulus. Following fusion of these cells eight different clones were isolated, all had reconstituted their capacity for IgE-mediated histamine release and had PMT I and PMT II enzyme levels which were 4-6 fold higher than in the parental variants. This is direct evidence to support a role for these enzymes in the cell secretory process. Therefore, the cloned variant sublines of the rat basophilic leukemia cell line offer a remarkable resource. Variants with drug resistant markers allow reconstitution experiments to characterize steps in the mechanism of histamine release.

Hybridomas are being produced which secrete monoclonal antibodies to a number of different antigens. A technique has been developed in this laboratory which dramatically improves the yield of antigen-specific hybridomas. The method is to transfer spleen cells from immunized animals into x-irradiated syngeneic recipients four days prior to cell fusion. Utilizing this system monoclonal antibodies were made against a number of different antigens. The monoclonal antibodies were used to distinguish two different fimbria on Actinomyces viscosus T14V; only one of these fimbria is involved in adherence. Therefore, further studies with these antibodies might help characterize the site(s) involved in coaggregation with S. mutans. In similar studies monoclonals have been produced to Cytophaga species, an organism which might be involved in destructive periodontitis. These organisms adhere to tooth root surfaces and the monoclonals are being tested for their ability to interfere with this binding. Other monoclonal antibodies have been produced to weak antigens. In one series of experiments hybridomas were prepared to the immunoglobulin E receptor on the rat basophilic cells; two of these antibodies appear to distinguish separate domains of the receptor, only one area of the receptor being critical in cell activation. Monoclonal antibodies have also been produced to the lymphokines; interleukin 1 and 2. These will provide useful tools to isolate the different lymphokines and to define their biological activities.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 DE-00007-21 LMI
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Studies on the Regulation of Carbohydrate Metabolism in Oral Bacteria		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Wittenberger, C. L. Jacques, N. Wolf, A. C.	Research Microbiologist Visiting Fellow Microbiologist	LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Microbiology Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md. 20205		
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SUMMARY OF WORK (200 words or less - underline keywords) Pathways of <u>carbohydrate metabolism</u> operative in <u>oral bacteria</u> and mechanisms by which cellular metabolism is regula- ted continue to be under investigation. Current emphasis is placed on 1) the char- acterization of streptococcal <u>glucosyltransferase</u> (GT) and 2) delineation of the mechanism underlying the inactivation of a cell-associated FT. The extracellular GT produced by <u>S. salivarius</u> has been resolved into two catalytic components by DEAE cellulose chromatography. GT-I produced a water-insoluble glucan from sucrose while GT-II catalyzed the synthesis of a water-soluble polymer. A mutant was iso- lated which had an impaired ability to produce water insoluble glucan. This mutant was found to lack the GT-I component, although it did possess GT-S. The data indi- cate that GT-I and GT-S are products of different structural genes. <u>S. salivarius</u> possesses a cell-associated <u>fructosyltransferase</u> (FT) that undergoes rapid inac- tivation under certain specified conditions. The inactivation process was time dependent and required Cu^{++} specifically. FT inactivation was blocked by incuba- ting cells at 40° for 60 minutes prior to their introduction into inactivation buffer. Our studies have shown that FT inactivation is mediated by one or more enzymes and preliminary data suggest that one of these is a protease.		

OBJECTIVES:

It is the continuing general purpose of this project to examine fundamental mechanisms by which the biochemical activities of the microbial cell are regulated and to delineate, where possible, the molecular basis for such regulation. This report is a summary of studies that were oriented specifically toward 1) characterization of the Streptococcus salivarius extracellular glucosyltransferase and 2) delineation of the mechanism of inactivation of the S. salivarius cell-associated fructosyltransferase.

METHODS EMPLOYED:

All are standard techniques routine to the type of studies herein described.

MAJOR FINDINGS:

Glucosyltransferase. The extracellular glucosyltransferase (GT) produced by various oral streptococci has been studied extensively in a number of different laboratories. It has, however, remained an elusive protein to characterize. It has not been conclusively established, for example, that the various glucan polymers it synthesizes from sucrose are products of a single enzyme. The GT produced by certain strains of Streptococcus mutans has, in fact, been fractionated by various techniques into two major catalytic components. An important unresolved question, therefore, is whether these components are actually different proteins, i.e., products of distinct structural genes or whether the disparate reaction products synthesized by them is due to an artifactual perturbation of some naturally occurring complex or aggregate during purification. We have employed a genetic approach in an attempt to shed light on this question as it relates to the extracellular GT produced by Streptococcus salivarius. This is an extension of a project initiated just over two years ago.

The crude extracellular S. salivarius GT was resolved into two catalytic components by DEAE-cellulose chromatography. One component (GT-I) eluted at about 0.16 M KCl and synthesized a water-insoluble glucan. The other (GT-S), eluted at 0.24 M KCl and synthesized a predominately water-soluble glucan polymer from sucrose. In this regard the S. salivarius GT behaved like the GT produced by S. mutans strain 6715. The polymers synthesized by the S. salivarius GT-I and GT-S components possessed different glucosidic linkages. The glucan produced by GT-S was extensively hydrolyzed by an α -1,6-specific dextranase (>65%). In contrast, the polymer produced by GT-I was much more refractory to the action of dextranase (<10% hydrolysis). Another difference between GT-I and GT-S was in their respective catalytic responses to primer dextran. The activity of GT-I was only slightly stimulated by dextran T10, whereas GT-S activity was highly dependent upon T10.

In an attempt to analyze the relationship between GT-I and GT-S, several mutants of S. salivarius were isolated which, on the basis of colonial morphology on sucrose plates, appeared to have an impaired ability to produce water-insoluble glucan. Direct assay of cell-free filtrates from mutant cultures confirmed this point. The crude extracellular GT produced by one of these mutants (strain 22-A) was analyzed by DEAE-cellulose chromatography as described above for the wild type GT. The GT-I component, which in the wild type eluted at 0.16 M KCl, was not detected in comparable column effluent fractions from 22-A. The mutant did, however, possess the GT-S component and, like wild type GT-S, it was eluted from the column at 0.24 M KCl. In addition, 22-A GT-S activity was almost completely dependent upon primer dextran as was found for wild type GT-S.

It was of interest to assess more critically whether strain 22-A was actually devoid of the GT-I component. Effluent fractions from the mutant DEAE column corresponding to the wild type GT-I activity region were pooled and subjected to SDS polyacrylamide gel electrophoresis. It was found that strain 22-A was missing both the GT-I activity and corresponding protein band that were present in the wild type GT-I component. The data strongly indicate, therefore, that the S. salivarius GT-I and GT-S components resolved by DEAE-cellulose chromatography are products of distinct structural genes.

Fructosyltransferase inactivation. Over the past several years, a body of data has accumulated which indicates that abnormal and non-functional bacterial proteins are recognized as such by the cell and are preferentially degraded. The biochemical mechanisms involved in the recognition and processing of these proteins, however, is incompletely understood. We have undertaken a study designed to contribute information relevant to this important cellular process.

Last year we reported on a cell-associated fructosyltransferase (FT) produced by S. salivarius that was rapidly inactivated under certain conditions. When inactivated FT preparations were released from the cell and analyzed by polyacrylamide gel electrophoresis, the enzyme appeared to have undergone proteolysis. We have continued to investigate this inactivation process as it occurs in resting cell suspensions and report here some properties of the system.

The inactivation of cell-associated FT was found to be completely dependent upon Cu^{++} , which exerted its maximum effect at a concentration of about 10 μM . Cu^{++} had no direct effect on FT catalytic activity at concentrations up to 1.0 mM. The Cu^{++} requirement was highly specific and none of the following cations were effective substitutes: Fe^{+++} , Al^{+++} , Mn^{++} , Zn^{++} , Mg^{++} , Co^{++} , Ni^{++} , Ba^{++} , or Sn^{++} .

We reported previously that a mixture of 19 amino acids added to cell suspensions completely blocked FT inactivation. When the amino acids were tested individually, only cysteine and histidine were effective in this capacity. Histidine prevented inactivation at a final concentration

of 50 μM . It appears that histidine and cysteine act by binding Cu^{++} , because their effect was reversed by increasing the concentration of the cation.

One or more components of the FT inactivation is heat labile. Cell suspensions incubated at 40° for periods up to 180 minutes prior to their introduction into inactivation buffer containing Cu^{++} showed a progressive loss of ability to inactivate FT. When the cell-associated FT was solubilized (see below) and incubated at 40° , no loss of catalytic activity was observed over the 180 minute incubation period.

Several attempts have been made to develop a cell-free system for studying the inactivation process. Cell-associated FT was solubilized by treatment of the cells with an N-acetyl-muramidase (M-1 enzyme). The FT released by this treatment was quantitatively recovered in the supernatant fluid after centrifugation at $163,000 \times g$ for 90 minutes. The cell-free FT, however, was completely stable when tested in the inactivation buffer containing Cu^{++} . Moreover, addition of the solubilized enzyme back to cell suspensions of the wild type or an FT-negative mutant failed to result in its inactivation. Solubilized FT was also completely stable when incubated in inactivation buffer with a crude, cell-free extract. These results indicate that one or more components of the inactivation system is associated with the cell membrane or cell wall. They further suggest that FT may have to be inserted into the membrane/wall before it can be acted upon by the inactivation enzyme(s).

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

Our continuing work on the regulation of bacterial metabolism is of broad biological significance. Intimate knowledge of specific biochemical control sites offers, for example, the potential for the rational design of new chemotherapeutic agents to control pathogenic bacteria. Such information is also invaluable for the construction and selection of mutants that could be of both commercial and medical importance. Current studies on the exoenzymes glucosyltransferase and fructosyltransferase are contributing specifically to our understanding of the role they play in the attachment and colonization of tooth surfaces by oral streptococci.

PROPOSED COURSE:

Our studies on the mechanism of inactivation of the cell-associated fructosyltransferase will receive special emphasis. We will undertake an examination of various membrane and other subcellular fractions as a possible source of the protease. The fructosyltransferase negative mutant should be very useful in this regard. It also seems likely from our present data that the cell-associated fructosyltransferase may require enzymatic "modification" before it is recognized as a substrate by the protease. We will, therefore, initiate studies designed to establish and characterize the modification system.

PUBLICATIONS:

1. Jacques, N. A. and Wittenberger, C. L. 1981. Inactivation of cell-associated fructosyltransferase in Streptococcus salivarius. J. Bacteriol., in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00022-15 LMI
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Comparative Physiology of Lactic Acid Bacteria and Other Oral Microbes		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
London, J. P. Hausman, S. Z. Kolenbrander, P.	Research Microbiologist Microbiologist Senior Staff Fellow	LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any) Roger Celesk, Dept. of Biology, University of Ohio at Dayton Harold Neimark, Downstate Med. Center, SUNY, Buffalo		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Microbiology Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md. 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) A group of mutants of <u>S. avium</u> and <u>L. casei</u> have been generated that are blocked at each step of <u>pentitol metabolism</u> . These mutants are being used to define and describe the components of the pentitol dissimilating system found in these two microorganisms. Thus the highly specialized soluble component of the <u>xylitol PEP-phosphotransferase system (PTS)</u> , namely Enzyme III, is being purified to homogeneity prior to its complete characterization. Similarly, the <u>NAD-specific xylitol-5-P dehydrogenase</u> is also being purified and characterized biochemically. In addition, these mutants are also being used to determine which intermediate products of pentitol metabolism are responsible for inducing the xylitol specific components of the PTS and the dehydrogenase. <u>Cytophaga</u> species isolated from subgingival plaque of patients with periodontitis have been <u>characterized biochemically</u> and shown to be facultative aerobes capable of inducing a functional tricarboxylic acid cycle. The organisms appear to be incapable of producing either gingivitis or bone loss when implanted in germ-free animal models. They have been shown to <u>coaggregate</u> with <u>Actinomyces israeli</u> , another inhabitant of the periodontal pocket.		

OBJECTIVES:

A) A study describing the sequence of induction, regulation and mechanism of action of the enzymes participating in pentitol metabolism is being continued. A group of mutants of Lactobacillus casei and Streptococcus avium that are blocked at the various steps in pentitol metabolism have been generated and these are being used to achieve the following:

1. Purify and biochemically characterize the soluble enzyme III component of the xylitol PTS.
2. Solubilize, purify and characterize the membrane bound enzyme II component of the xylitol PTS.
3. Purify and characterize the NAD xylitol D-arabitol-5-P dehydrogenase.
4. Determine which intermediate products act as inducers for the respective enzymes of the pentitol pathway.

B) A physiological and ecological study of the oral Cytophaga species is underway in the following areas:

1. A determination of how these cells regulate carbon flow through the bifurcated TCA cycle during anaerobic growth so that succinate rather than α -ketoglutarate accumulates.
2. Determine the nature of the receptor sites responsible for adherence to hydroxyapatite-containing surfaces and coaggregation with A. israelii.
3. Estimation of numbers of Cytophaga sp. in the periodontal pocket to establish significance of microbes to periodontal disease.

METHODS EMPLOYED:

Conventional immunological, biochemical and bacteriological methods were employed in the studies reported here.

MAJOR FINDINGS:

A. pentitol dissimilation by lactic acid bacteria. The enzyme III component of the xylitol PTS is currently being purified and characterized. It appears to be a small basic and hydrophobic protein with an approximate molecular weight of 24,000. Low ionic strength solutions are necessary to stabilize its activity and it can be stored for long periods of time under these conditions. High ionic strength media, greater than 0.1 M, cause the protein to aggregate in micelles with a molecular weight greater than 200,000. A complete purification is now being attempted using a variety of chromatographic techniques. Similarly, the xylitol/D-arabitol-5-P dehydrogenase of L. casei C183 and the ribitol-5-P dehydrogenase of L. casei CL-16 are currently being purified and characterized.

Specific substrates for these enzymes, namely, xylitol-5-P and ribitol-5-P have been synthesized chemically while D-arabitol-5-P has been synthesized biologically. Thus far, both xylitol-5-P and D-arabitol 5-P dehydrogenase activity of L. casei C183 is associated with a single activity peak in DEAE and Sephacryl chromatography having an estimated molecular weight of 168,000. Ribitol-5-P dehydrogenase of L. casei CL-16 has an estimated molecular weight of 100,000.

Preliminary mutant analyses indicate that the induction process of the xylitol PTS and dehydrogenase is very complex. It is not yet known whether the structural genes for Enzyme II, Enzyme III or dehydrogenase are arranged as an operon or a regulon, however, the data indicate that the L. casei xylitol system possesses three regulatory gene products specific for the inducers xylitol-5-P, D-arabitol-5-P and xylulose-5-P, respectively. It was also possible to isolate mutants missing each of the three specific enzymes necessary to convert xylitol to a product of the pentose pathway. These mutants were used to confirm the existence of a specific enzyme II and III for the phosphotransferase system.

C. Biochemical and Ecological studies with the oral Cytophaga species.

The oral cytophaga resemble other facultatively aerobic bacteria in that they can be adapted to grow in air and respire glucose. Cultures that have been adapted to aerobic growth possess a function tricarboxylic acid cycle. The enzyme α -ketoglutarate dehydrogenase is induced in the presence of air and permits the TCA cycle to function effectively. However, such cultures readily revert to anaerobiosis.

Recently, the Cytophaga species have been shown to coaggregate with certain strains of Actinomyces israelii. The interaction is not reversed by lactose and the reaction appears to be mediated by a heat sensitive component found on the cell wall of the gram negative cytophaga. The experiments are being carried out in collaboration with Dr. Paul Kolenbrander.

SIGNIFICANCE TO BIOMEDICAL RESEARCH:

The utilization of pentitols by lactic acid bacteria appears to be a rare trait that is presently limited to one species of Streptococcus, S. avium and twenty percent of all Lactobacillus casei strains tested thus far. However, if the transfer of genetic material among lactic acid bacteria, especially interspecific transfers, occurs with any frequency, the current use of pentitol sugar substitutes will eventually select for populations of oral streptococci and lactobacilli capable of using these substrates for the production of lactic and acetic acid. It is important, therefore, to determine how these organisms regulate and metabolize pentitols.

It is not yet known whether Cytophaga sp. actively participate in the onset of chronic periodontal disease. However, their ability to glide about and subsequently colonize the tooth root surface assures their presence in the periodontal pocket. The endotoxin present in their outer membrane may contribute to the massive immunological response observed in cases of chronic periodontitis.

PROPOSED COURSE OF RESEARCH

A. Enzyme III of the xylitol PTS will be purified to homogeneity and characterized biochemically and physically. The manner in which it functions in apposition to HPr will be determined. The protein will then be used as an antigen to prepare antisera to determine its similarity to other enzyme III components found in lactic acid bacteria.

The xylitol-5-P and ribitol-5-P dehydrogenases will be purified and characterized biochemically and physically. Its regulation and kinetic properties will be studied and antisera prepared against it.

A complete characterization of mutants will be performed. Antisera prepared against Enzyme II, Enzyme III and xylitol-5-P dehydrogenase will be used to determine whether the mutations have occurred in the mutants regulatory or structural genes. With these data on hand, a better understanding of the induction mechanism should be realized.

B. An analysis of the outer membrane of Cytophaga sp. will be performed to identify the receptor sites responsible for adherence to hydroxyapatite as well as the coaggregation reaction with A. israelii. The regulation of the six carbon segment of the TCA cycle will be studied to learn why this portion of the cycle is not active during anaerobic growth.

One of the TCA enzymes will be selected for purification and used as an evolutionary marker to determine whether the oral Cytophaga sp. are related to the soil and aquatic myxobacteria.

PUBLICATIONS:

1. Celesk, R. A. and J. London. Attachment of oral Cytophaga species to hydroxyapatite containing surfaces. *Infect. Immun.* 29: 768-777, 1980.
2. Chace, N. M., B. Sgorbati and J. London. A comparison of the physical and biochemical properties of NAD-dependent glyceraldehyde-3-phosphate dehydrogenases from three lactic acid bacteria. *Zbl. Bakt. Hyg.* (in press).
3. Sgorbati, B. and J. London. Demonstration of phylogenetic relatedness among members of the genus Bifidobacterium using the enzyme trans-aldolase as an evolutionary marker. *Intern. J. Sys. Bacteriol.* (in press).
4. Neimark, H. and J. London. Origins of the mycoplasmas: Sterol-non-requiring mycoplasmas evolved from streptococci. *Proc. Natl. Acad. Sci.* (in press).
5. London, J., R. Celesk, and P. Kolenbrander. Physiological and ecological properties of the oral gram negative gliding bacteria capable of attaching to hydroxyapatite. In "Host Bacterial Interactions in Periodontal Disease" (S. Mergenhagen and R. Genco eds.) (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00042-11 LMI
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Utilization of Carbohydrates by Oral Bacteria		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Chassy, B. M. Porter, E. V. Hull, E. Rokaw, E. Thompson, J. Lee, Y. A.	Research Chemist Chemist Biological Lab Aide Chemist Expert Visiting Fellow	LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Microbiology Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md. 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
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<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The <u>metabolism of sucrose, galactose</u> <u>and lactose</u> by lactic acid bacteria were studied. Sucrose-PTS, sucrose 6-phos- phate hydrolase and mannofructokinase activities were characterized in <u>Strepto-</u> <u>coccus lactis</u> . Sucrose induced expression of the <u>PTS</u> and hydrolase activities but mannofructokinase was expressed after growth in the presence of sucrose or any growth carbohydrate not transported by a PTS mechanism. A system for <u>conjugal</u> <u>transfer of lactose plasmids</u> among <u>Lactobacillus casei</u> strains was developed. From the results of this, and other studies, it appeared that the plasmids encoded the lactose-PTS and <u>phospho-β-galactosidase</u> . These results have been confirmed by the <u>molecular cloning</u> of lactose plasmid DNA into <u>Escherichia coli</u> . <u>Recombinant clones</u> containing a 7.9 Kbp insert of Lactobacillus plasmid DNA in the PTS I site of pBR322 expressed cloned phospho-β-galactosidase activity. <u>Lactobacillus</u> lactose plasmids were found to have considerable DNA-DNA homology even though the <u>restriction endonuclease</u> digestion fragment patterns varied greatly. A unique galactose-specific PTS has been isolated from <u>L. casei</u> .		

OBJECTIVES:

1. One objective of this study is to understand how carbohydrates are transported and metabolized by various oral streptococci and lactobacilli. Primary attention has been devoted to the pathways of sucrose and lactose dissimilation, but ultimately the mechanisms underlying the fermentation of all carbohydrates will be of interest.
2. A second major objective has been to determine the role played by plasmids in the adaptation of oral bacteria to their unique ecosystem. It should also be possible to utilize plasmids and recombinant DNA technology as tools for the genetic and biochemical analysis of metabolic pathways, and the regulation of gene expression.

MAJOR FINDINGS:

A. Characterization of sucrose 6-phosphate hydrolase in Streptococcus mutans.

Previous studies in this laboratory had shown that strains of S. mutans representing the seven major serotypic groups all possess a sucrose 6-phosphate hydrolase. The enzyme cleaves sucrose 6-phosphate formed as a result of transport and phosphorylation of sucrose by the sucrose PTS. The products formed are glucose 6-phosphate and fructose. The fructose moiety enters glycolysis as fructose 6-phosphate after phosphorylation by a highly specific ATP-dependent mannofructokinase that was previously isolated and characterized in this laboratory. The purified preparations of sucrose 6-phosphate hydrolase also displayed a slight hydrolytic activity toward high concentrations of sucrose. This activity was originally reported by other investigators to be an intracellular invertase. The co-purification of these two activities in all strains of S. mutans studied, their co-incident electrophoretic mobility, and the absence of other fractions containing invertase activity confirm the conclusion that the intracellular invertase is a minor catalytic activity of sucrose 6-phosphate hydrolase. The physical characteristics of the hydrolases isolated from various strains were similar; molecular weights ranged from 38-43,000 and the electrophoretic mobility in polyacrylamide and SDS-polyacrylamide gels were comparable, though not identical. A greater variability was observed in kinetic properties; K_m values varied from 0.015 to 0.3mM. These results indicate that S. mutans strains have similar pathways of metabolizing sucrose intracellularly, but that there may be some evolutionary divergence or diversity in the protein structures involved.

B. Sucrose Metabolism in Streptococcus lactis.

Streptococcus lactis is closely related to the pathogenic oral streptococci and can gain easy access to the oral cavity through ingestion of dairy products yet appears to be non-pathogenic to man. In light of their similarities, a study was undertaken to determine if the metabolism of sucrose by S. lactis and S. mutans were similar. Intact cells of S. lactis cultured on sucrose were treated with iodoacetate to block glycolysis and cause the accumulation of 35-40mM intracellular PEP. These cells

rapidly transported ^{14}C -sucrose at the expense of PEP; however cells grown with glucose, fructose or lactose did not transport sucrose. Sucrose 6-phosphate was identified as the primary intracellular product. It appeared that this intermediate was rapidly metabolized to fructose, fructose 6-phosphate, glucose 6-phosphate, and fructose 1,6-diphosphate. These results demonstrated the presence of both a sucrose PTS and a system capable of hydrolysis of sucrose 6-phosphate. The starved cells were essentially devoid of ATP, but the appearance of fructose 6-phosphate hydrolysis or glucose 6-phosphate (formed from sucrose 6-phosphate hydrolysis) caused an *in vivo* activation of pyruvate kinase to produce ATP from endogenous PEP reserves. Sucrose 6-phosphate hydrolase was isolated from sucrose cultured cells and purified to homogeneity by DEAE-cellulose and Sephacryl S-200 column chromatography. Its apparent molecular weight was 28,000; smaller than that found in *S. mutans* (see under "A" above). The K_m for sucrose 6-phosphate, 0.1mM, was comparable to that found for the purified enzyme isolated from *S. mutans* (see under "A" above). A mannofructokinase similar to that characterized in *S. mutans* was partially purified from cell-free extracts of *S. lactis* by the same methods and found to have a molecular weight of 42,000 (*S. mutans* SL-1 mannofructokinase; 49,000). The K_m for mannose was 0.24mM, for fructose 0.33mM and for ATP 0.22mM (compared with fructose K_m 0.63mM and mannose 0.37mM found with *S. mutans* SL-1). Thus, the pathway of sucrose metabolism in *S. lactis* and *S. mutans* appears similar and the soluble enzymes involved fairly comparable in properties. While sucrose was necessary as a growth substrate for induction of the sucrose PTS and sucrose 6-phosphate hydrolase, expression of mannofructokinase activity was derepressed not only by growth on sucrose, but after growth on any sugar not transported by a PTS mechanism. This finding implied a role for PTS systems in regulation of the expression of certain enzymes.

C. Regulation of PTS Activity and Regulatory Effects by PTS Activity in Lactic Acid Bacteria

In order to examine regulation of PTS activity and regulation of other biochemical processes by the PTS system, the metabolism of several sugars and sugar analogs by various strains of *S. lactis* and *L. casei* was evaluated. It was found that 2-deoxyglucose resistant mutants lacked a functional glucose PTS, although they were capable of growth on glucose at rates comparable to the wild type strains. These mutants, in contrast to the wild types, were also found to carry out a heterolactic fermentation of glucose. The mutants were derepressed with respect to expression of mannofructokinase and phospho- β -galactosidase. These results indicated that the presence of a functional glucose-PTS was required for the repressive effects of glucose to be exerted. These observations were confirmed in an unusual strain of *S. lactis* which was found to regulate the activity of the glucose-PTS. In the presence of 2-deoxyglucose this strain transported glucose by an alternate mechanism and excluded 2-deoxyglucose. Its properties in the presence of 2-deoxyglucose resembled those of a resistant mutant; it carried out a heterolactic fermentation of glucose and was derepressed for the expression of phospho- β -galactosidase and mannofructokinase.

During the course of this study it was found that 2-deoxyglucose resistant mutants were not completely resistant to the analog. While growth of the mutants on a variety of fermentable sugars proceeded normally in the presence of 2-deoxyglucose, no growth was observed on fructose, glucosamine or ribose. An examination of this unusual effect revealed that 2-deoxyglucose does not necessarily have to block metabolism to inhibit growth and that there exists a mechanism for promoting the rapid efflux of 2-deoxyglucose.

Current studies are directed at determining the mechanism of regulation of expression exerted by PTS system, the mode of action of 2-deoxyglucose as an inhibitor, and the nature of the 2-deoxyglucose expulsion system. This, and the foregoing study, are being conducted in collaboration with Dr. John Thompson of the New Zealand Dairy Research Institute, currently serving as an expert in the Microbiology Section.

D. Plasmid Associated Lactose Metabolism in L. casei.

In previous studies, we demonstrated that lactose metabolism in most strains of L. casei depends on the presence of strain-specific lactose plasmids that vary in mass from 17.5 to 42 MDalton. Strains cured of their lactose associated plasmid lose the ability to express the lactose-PTS and phospho- β -galactosidase. Analysis of restriction endonuclease digests of lactose plasmid DNA by agarose gel electrophoresis revealed that the plasmids share very few fragments of common size and are structurally quite dissimilar. Recent experiments using the Southern Blot Technique have demonstrated that a high degree of DNA-DNA homology exists between the various lactose plasmids. These data point to the presence of common sequences of DNA arranged in alternate orders and perhaps spaced by heterologous intervening sequences. Three different kinds of experiments have demonstrated that at least two structural genes are a common feature of the lactose plasmids. First, lac- strains of S. sanguis (obtained from Dr. E. J. St. Martin) were transformed to the lac+ character with these plasmids. Secondly, a system for the conjugal transfer of lactose plasmids from lac+ to lac- L. casei strains has been developed. Recipient strains carry the plasmid present in the donor and ferment lactose with the characteristics of the donor, but retain all other phenotypic characteristics of the recipient. The final, and most conclusive, evidence for the presence of specific structural genes on the lactose plasmids derived from the molecular cloning of Lactobacillus lactose plasmids into Escherichia coli. The 23 MDal lactose plasmid from strain 64H was digested with PST I and ligated into the PST I site that lies in the ampicillin resistance determinant of pBR322. The ligation mixture was used to transform E. coli X1849. Tetracycline resistant, ampicillin sensitive clones were selected and examined for the presence of recombinant plasmids. One of the recombinant clones selected, which carried a 7.9 Kbp insert of Lactobacillus DNA in pBR322, expressed phospho- β -galactosidase in E. coli. This finding not only confirmed the presence of this structural gene on the plasmid, but also demonstrated that Lactobacillus DNA can express in the E. coli host system. Mapping and other cloning data, gathered with other restriction enzymes and vectors, indicated that the phospho- β -galactosidase gene contains within it a BamH I and EcoR I

site. The restriction endonuclease map of the cloned fragment indicates several sites which may be used for subcloning. The subcloned fragment can now be used as a specific probe for the presence of phospho- β -galactosidase genes in other strains and species.

E. Identification of a Specific Galactose-PTS in L. casei.

In S. lactis and Staphylococcus aureus galactose can be transported by the lactose PTS. Inhibition of the lactose PTS by parachloro-mercuribenzoate has revealed an underlying residual activity toward galactose, but a specific galactose-PTS has not been isolated. Lac- strains of L. casei were found to retain galactose-PTS activity suggesting the presence of a discreet galactose PTS. Cells were disrupted with a bead mill and fractionated into a soluble cytoplasmic fraction and a membrane fraction. Both fractions were isolated from galactose grown cultures; similar fractions from glucose cultured cells or mixtures of the two fractions from glucose and galactose grown cultures could not phosphorylate galactose. These results indicated the presence of both an inducible membrane associated and an inducible soluble galactose-specific factor analogous to the Enzyme II lactose and factor II lactose. The molecular weight of the soluble factor was estimated by gel-filtration to be 35,000. The product of the reaction was determined by paper chromatography and ion-exchange chromatography to be galactose 6-phosphate. Soluble supernatants also contained an ATP-dependent galactokinase which produced galactose 1-phosphate. These results demonstrated that a unique high affinity galactose-specific PTS exists in L. casei. The presence of galactokinase and a galactose PTS, producing galactose 1-phosphate and galactose 6-phosphate respectively, indicates that two pathways for the dissimilation of galactose may be present. The relative importance of these two pathways is currently being evaluated.

SIGNIFICANCE TO BIOMEDICAL RESEARCH:

The mechanism of carbohydrate utilization by oral microbes has doubtless been an important selective factor in their evolutionary development. These studies underscore the diverse and complex adaptation of these organisms to efficiently utilize carbohydrates. Ultimately, such studies should allow us to understand the economy of these organisms and may suggest changes that can be made in the oral environment that would favor shifts in the ability of the ecosystem to support a benign rather than a pathogenic microflora. Of particular importance are insights gained into the mechanism of regulation of pathways and gene expression.

Considering the demonstrated role of plasmids in coding for pathogenic potential, conferring antibiotic resistance, as well as coding for antigen and bacteriocin production in other bacteria, it would be of great value to know if such relationships exist between plasmids and the oral microflora. In addition, a study of the distribution, function and relatedness of these plasmids may contribute to our understanding of bacterial evolution, specialization, and adaptation in an emerging and changing ecosystem. The development of molecular cloning systems not only allows detailed examination of gene structure and function, but also opens the way for genetic manipulation of oral lactic acid bacteria by recombinant DNA techniques.

PROPOSED COURSE:

1. To continue to investigate mechanisms of regulation of gene expression in the lactic acid bacteria.
2. To evaluate the mechanism of 2-deoxyglucose inhibition of growth, the expulsion of non-metabolizable analogs and the role of PTS activity in regulating gene expression in lactic acid bacteria.
3. To complete the in vivo and in vitro characterization of the galactose PTS, and determine the relative role played by the two metabolic pathways for galactose.
4. To conduct experiments designed to subclone phospho- β -galactosidase and to clone PTS components from Lactobacillus into E. coli.
5. To initiate a project directed at development of a transformation system in Lactobacillus and to exploit it for molecular cloning and genetic engineering.

PUBLICATIONS:

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2. Chassy, B. M. and Porter, E. V. (1981). "Sucrose 6-Phosphate Hydrolase" in Methods in Enzymology, in press.
3. Porter, E. V. and Chassy, B. M. (1981). "Glucokinase" in Methods in Enzymology, in press.
4. Thompson, J. and Chassy, B. M. (1981) "Uptake and Metabolism of Sucrose by Streptococcus lactis K1" (1981). J. of Bacteriol. in press.
5. Chassy, B. M. and Rokaw, E. (1981) "Conjugal Transfer of Plasmid Associated Lactose Metabolism in Lactobacillus casei subsp. casei" in Plasmids (Plenum Press), in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00043-11 LMI									
PERIOD COVERED October 1, 1980 - September 30, 1981											
TITLE OF PROJECT (80 characters or less) Physiological and Genetic Studies on Pathogenic Oral Microorganisms											
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Donkersloot, J. A.</td> <td style="width: 33%;">Research Microbiologist</td> <td style="width: 33%;">LMI NIDR</td> </tr> <tr> <td>Harr, R. J.</td> <td>Bio Lab Tech (Micro)</td> <td>LMI NIDR</td> </tr> <tr> <td>Hull, E. M.</td> <td>Bio Lab Aid</td> <td>LMI NIDR</td> </tr> </table>			Donkersloot, J. A.	Research Microbiologist	LMI NIDR	Harr, R. J.	Bio Lab Tech (Micro)	LMI NIDR	Hull, E. M.	Bio Lab Aid	LMI NIDR
Donkersloot, J. A.	Research Microbiologist	LMI NIDR									
Harr, R. J.	Bio Lab Tech (Micro)	LMI NIDR									
Hull, E. M.	Bio Lab Aid	LMI NIDR									
COOPERATING UNITS (if any) Dr. Donald J. LeBlanc, NIAID, NIH											
LAB/BRANCH Laboratory of Microbiology and Immunology											
SECTION Microbiology Section											
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md.											
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:									
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS											
SUMMARY OF WORK (200 words or less - underline keywords) <u>Plasmids</u> from oral <u>streptococci</u> and their role in the physiology and ecology of this group of organisms are under investigation. Within this context, a multiple <u>antibiotic</u> resistant strain of <u>Streptococcus mutans</u> (19S), originally isolated from the jaw of a pig, is being characterized. This isolate transferred, by conjugation, only its <u>tetracycline</u> <u>resistance</u> to two strains of <u>S. faecalis</u> and to one other strain of <u>S. mutans</u> . This transfer was always accompanied by the appearance of an 8 megadalton plasmid (with a copy number of 1) in the transconjugants. However, such a plasmid has, so far, not been identified in the original <u>S. mutans</u> host, 19S. Presently, we are using the Southern <u>hybridization</u> method, with plasmid DNA from one of the transconjugants as the labeled probe, to ascertain whether the tetracycline resistance gene in the original 19S host is on the chromosome or on a plasmid that cannot be detected by the methods used. Preliminary results suggest that the latter may be the case.											

OBJECTIVES:

The general objective of these studies continues to be the characterization of plasmids in oral streptococci, with special emphasis on S. mutans. Specifically, the studies conducted this year were designed to characterize a multiple antibiotic resistant strain of S. mutans. Historically, multiple antibiotic resistance is often encoded on plasmids. However, the particular strain of S. mutans being examined did not appear to contain a plasmid, yet, preliminary experiments showed that one of the antibiotic resistance markers was transmissible to other streptococci. Interestingly, plasmid DNA was detected in the transconjugants that had become antibiotic resistant. Because no other system has been described with these general features, our current objective has been to characterize the system in detail. This report summarizes the progress made this year.

METHODS EMPLOYED:

An early version of a new method to purify plasmid DNA from streptococci was described in last year's report. This method has been refined and scaled up so that one liter batches of culture can now be rapidly enriched for plasmid DNA. The salient feature of the method is an alkali treatment at pH 12.1 to simultaneously lyse the cells and denature chromosomal DNA. This method was successfully used to demonstrate plasmid DNA in various tetracycline resistant transconjugants; however, it did not reveal a plasmid in the original multiple antibiotic resistant strain of S. mutans used in this study. Because of this, a second method was developed that uses thermal denaturation of chromosomal DNA (because of its closed structure, plasmid DNA is more thermostable than linear DNA). The details of this method were developed using the pAM7 plasmid from S. mutans LM-7.

The other methods used have been described before.

MAJOR FINDINGS:

In last year's report we described preliminary findings on a multiple antibiotic resistant strain of S. mutans. This strain, 19S, was originally isolated from the jaw of a pig that had been maintained on tetracycline supplemented feed. Strain 19S is highly resistant to four antibiotics; erythromycin, lincomycin, tetracycline, and streptomycin. In streptococci, resistance to both erythromycin and lincomycin is typically due to a plasmid. However, so far we have not detected a plasmid in this strain, despite numerous attempts employing a variety of different methods (for details, see the Methods section). Notwithstanding this, mating experiments showed that of the four resistances, only the tetracycline resistance was transmissible to other streptococci by a conjugation-like process. Transfer of tetracycline resistance from the porcine isolate 19S to a human isolate S. faecalis (strain JH2-2) occurred during matings on membrane filters at a frequency of 2×10^{-5} per donor colony forming unit. This interspecies transfer also took place in liquid culture at a frequency of 10^{-5} . The transfer in liquid occurred relatively fast (1-2 hr) and was not inhibited by DNase. Cell-free filtrates were not active; therefore, the process resembled conjugation.

Sex factors (as described by Clewell's group) did not appear to play a role in this particular system. Analysis of the tetracycline resistant transconjugants for plasmid DNA showed a weak band after electrophoresis that was absent in the original recipient (JH2-2). CsCl-ethidium bromide centrifugation showed that this band was indeed plasmid DNA. Based on its electrophoretic mobility, the size of this plasmid (pDJ2) was 8 ± 2 Mdal. We noted that these transconjugants spontaneously lost their resistance at low frequency. Sensitive derivatives were devoid of pDJ2, which proves that this plasmid actually encodes tetracycline resistance in the transconjugants.

S. mutans 19S also transferred its tetracycline resistance to another strain of S. mutans (6715-10). This transfer took place only during anaerobic matings on membrane filters, and the frequency was much lower (2×10^{-8}) than when JH2-2 was the recipient. Transconjugants from this mating also harbored pDJ2 and, in turn, donated their resistance, and pDJ2, to S. faecalis JH2-2. Thus, it appears that this relatively small plasmid is able to mobilize itself, and that it encodes at least some transfer functions. It should be mentioned that these results represent the first example of an indigenous trait that is transmissible among oral streptococci.

Recently, several investigators have reported transfer of antibiotic resistance from the chromosome of one strain of Streptococcus to that of another without the apparent involvement of plasmids. It is clear that our findings do not fall in this category, because all transconjugants contained pDJ2. Since we did not find a plasmid in the original host, one working hypothesis has been that the tetracycline resistance is encoded on the chromosome of strain 19S, but that it is able to excise, transfer, and replicate independently in the transconjugants. To prove that the tetracycline resistance is indeed on the chromosome, one needs to purify pDJ2 and show that it hybridizes to the 19S chromosome. Efforts to purify the required amount of plasmid (about 1 μ g) by conventional CsCl-ethidium bromide centrifugation followed by sucrose gradient centrifugation have not been successful. Several reasons for this have become apparent: The yield of pDJ2 from the transconjugants was very low (about 0.2-0.4 μ g per liter of culture); this necessitated concentration of partially purified plasmid preparations about 10 times more than is usual, which resulted in the copurification of some denatured chromosome and intracellular polysaccharide with pDJ2 on the density gradients used. In the hope of obtaining a better yield of plasmid, transconjugants from a recombination-deficient mutant of JH2-2 (UV202) and from S. faecalis OG1 were isolated and studied. However, the yield of pDJ2 was not significantly greater from these isolates. Presently, we are successfully using preparative electrophoresis followed by extraction of the plasmid from the agarose as a means to obtain enough pure plasmid for labeling by nick-translation. This probe will be used to establish (by Southern hybridization) whether the tetracycline resistance in S. mutans 19S is actually encoded on the chromosome, or whether it is on a plasmid that cannot be visualized by the other methods used.

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

Streptococci are etiological agents of numerous human infections, some of which are life threatening. Although most streptococci are sensitive to penicillin, resistance to other potentially useful antibiotics such as erythromycin, lincomycin, and tetracycline occurs at significant frequencies. Even though it has become apparent that not all antibiotic resistance in Streptococcus is due to plasmids, it is also quite clear that knowledge about streptococcal plasmids and about the transmission of antibiotic resistance between individual streptococci is highly significant from a clinician's viewpoint.

Studies on plasmids are also of interest from a basic biological viewpoint. In the genus Streptococcus, plasmids were discovered less than 10 years ago, and it has recently become evident that there are some significant differences between these plasmids and those in gram-negative bacteria. Our studies contribute to this rapidly expanding area of scientific endeavor. In fact, our results represent the first example of an indigenous trait in an oral Streptococcus that is transmissible. In addition, our studies bear heavily on the question of chromosomal versus plasmid-mediated antibiotic resistance.

With respect to dental practice per se, tetracycline is used in the management of certain cases of periodontal disease. Consequently, knowledge about the transmission of tetracycline resistance between oral streptococci is of importance for the proper therapeutic use of this antibiotic.

Our studies are also significant from a public health viewpoint. It is quite likely that the widespread use of antibiotics in animal husbandry has given rise to an animal reservoir of bacteria resistant to antibiotics. Our studies clearly show that transfer of antibiotic resistance from an animal isolate (19S) to a human isolate (JH2-2) can take place. This is of considerable concern for the development of policy on the proper use of antibiotics in animal feedstocks.

PROPOSED COURSE OF STUDIES:

The studies on the multiply antibiotic resistant S. mutans 19S will be continued. Specifically, we propose to determine:

1. The location of the genes responsible for tetracycline and erythromycin resistance in S. mutans 19S (chromosome or plasmid?). As a probe for the hybridization experiment to locate the tetracycline resistance gene, we will use pDJ2, which is now being purified by preparative electrophoresis. The possibility of cloning the tetracycline resistance gene from pDJ2 into Escherichia coli to facilitate the making of a probe, is being considered. As a probe for the erythromycin resistance we will use a small derivative (and/or a restriction fragment) of the streptococcal beta plasmid (which encodes erythromycin-lincomycin resistance).
2. If transmission of antibiotic resistance occurs between streptococci in an animal model system. These studies will be conducted in collaboration with Dr. W. Bowen (NCP, NIDR).

3. If pDJ2 bears resemblance to tetracycline resistance plasmids from gram-negative organisms. This will allow us to determine if evolutionary relationships between plasmids from widely divergent bacteria exist.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00096-07 LMI
PERIOD COVERED October 1, 1980 through September 31, 1981		
TITLE OF PROJECT (80 characters or less) Monitored and Modulated Therapy for Crevicular Infections of the Human Dentition		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Keyes, Paul H. Krichevsky, M. Rogosa, M. Rams, T. Howard, Suyu Love, L.	Dental Director Research Chemist Scientist Emeritus Staff Fellow Health Tech. (Dental) Technical Info. Spec.	LMI IR IR IR LMI IR
		NIDR NIDR NIDR NIDR NIDR NIDR
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Microbiology Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, MD 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
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<input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Distinct <u>qualitative</u> differences in <u>microbial populations</u> present in <u>sub-gingival plaque</u> samples were seen using phase phase-contrast microscopy in a) subjects with excellent <u>periodontal health</u> , b) subjects with <u>marginal gingivitis</u> and no pocket formation, and c) subjects with <u>destructive periodontitis</u> . The microbiological status observed in perio- dontal health characteristically presented with loosely organized "thread" forms coated with small cocoidal forms. Spirochetes and other large motile forms were never seen and few white blood cells were observed. In non-destructive marginal gingivitis, denser masses of thread forms and cocci were seen, as well as, occa- sional clusters of unorganized spirochetes and motile rods. White blood cells were observed, but only in the range of + 100 per field. In persons with destruc- tive periodontitis, large populations of motile bacteria and white blood cells in a too-numerous-count range were noted, in addition to large static masses of fil- aments, rods and cocci. The motile forms consisted of spirochetes, various rods and amoebae. Based on our findings, we suggest that both diagnosis and manage- ment of periodontal lesions can be improved by use of phase contrast microscopy to monitor the microbiological status of diseased sites.		

OBJECTIVES:

This study was undertaken to determine whether examination of crevicular plaque specimens with a phase contrast microscope would disclose any consistent qualitative differences between disease-associated samples and health-associated specimens, i.e., whether the bacterial populations recovered from root surfaces adjacent to inflamed periodontal tissues would show characteristic differences from those adjacent to healthy tissues. Such differences, if reproducible, could provide a useful tool for the diagnosis of disease and for monitoring various therapeutic regimens being tested for the control of disease.

METHODS EMPLOYED:

A phase contrast microscope was used to examine the microbiotae present in plaque from the crevicular surfaces of 12 persons with no evidence of periodontal inflammation (5 males and 7 females between 10 and 55 years of age). Examinations were also made of samples removed from radicular surfaces of 4 females and 8 males between 50 and 95 years of age who had marginal gingivitis but no clinical or radiographic evidence of destructive periodontitis, and from 30 patients who presented with typical signs of destructive periodontitis. Samples were taken with a curette and quickly transferred to a drop of tap water on clean microscope slides. The specimens were then covered with a cover slip and lightly compressed to spread them for satisfactory examinations at 600 and 1000x with a phase contrast microscope. Every effort was made to examine the bacterial complexes "intact" after removal from the circumradicular spaces. Ten or more fields of outer surface aggregates were examined, notations were recorded, and video tape recordings were made of representative fields to permit a review of findings and independent evaluations by other observers.

MAJOR FINDINGS:Bacterial Patterns in Periodontal Health.

Microscopic examination of plaque samples from persons with excellent periodontal health revealed a consistent and typical bacterial pattern. The pattern consisted of bacterial aggregations dominated by a loosely organized network of filamentous microorganisms or "thread forms". Shapes typical of actinomycetes were predominant. The "thread forms" appeared to be partly colonized by coccoidal forms and other very small microorganisms. On occasion, a few very small and highly motile coccus-like cells were seen darting around in erratic circles independent of the filamentous network. Spirochetes or other larger motile forms were never observed in any of the plaque samples taken from healthy mouths and no turbulence (as will be described later) was observed on the surface of the bacterial aggregations. Overall, the bacterial pattern in periodontal health consisted of a static and stationary network of microorganisms where occasionally a few white blood cells were found adjacent to the network.

Bacterial Patterns Found In Marginal Gingivitis. In samples taken from older persons (50 years of age) with marginal gingivitis, the bacterial patterns were consistently different from those seen in periodontal health. Greater aggregations of bacteria and a wider variety of microbial types were seen; both motile and non-motile forms were observed. The

non-motile microorganisms formed a static mass composed of complex networks of filamentous forms colonized by coccoidal and other small forms. The outer surface of this mass was not compactly organized. In fields adjacent to the static configurations, motile organisms were found in all cases except one, a finding that was significantly different from samples taken from healthy mouths.

Of the motile organisms observed in marginal gingivitis, the most common morphological types were rods. Smaller rods (2 x 3-5 microns) were seen that moved by a rapid rotary motion at one end, and in occasional fields these were present in numbers too-numerous-to-count. Thin flexing rods that glided slowly were found in eight patients. After affixing one of themselves to the glass surfaces, they moved rapidly in clockwise or counter clockwise arcs. These forms have been identified as strains of Cytophaga.

In 11 of 12 cases, spirochetes were seen, although they formed a relatively minor part of the bacterial congregations. More than 50 spirochetes in a field were rarely seen and many fields showed none. White blood cell levels were not as high as expected from the appearance of the tissues. In some fields there were five to ten white blood cells, and in only a few fields were there 100 or more.

Characteristically, the bacterial pattern present in marginal gingivitis was that of static or stationary masses of filaments and coccoidal forms associated with various types of motile forms, including rods and spirochetes. However, motile forms were neither highly organized in their relationships to one another or in their patterns of activity (motion).

Bacterial Patterns In Periodontitis. Complex, highly organized, aggregations of microorganisms were found in samples removed from root surfaces adjacent to pockets in patients with typical signs of chronic destructive periodontitis. The bacterial aggregations exhibited a degree of organization and behavior that was not seen in states of periodontal health or marginal gingivitis.

In these microbial complexes, both motile and non-motile organisms were present. The stationary microorganisms formed a densely aggregated static mass that had associated with it long, branching, sometimes twisted, rope-like chains of rods colonized by layers of coccoidal forms. These structures apparently extended into the circumradicular spaces where they provided surfaces for motile forms to congregate and organize.

Motile microorganisms constituted the most outstanding and distinctive features of the subgingival complexes. Plaques from pockets showed motile bacteria that were highly organized in their collective behavior. In typical fields great numbers of long and thick spirochetes formed dense, highly turbulent, brush-like coatings on the static mass by affixing one end to the outer surface of the mass. These organized congregations of rods and spirochetes have been described as "brush patterns" and were seen only in persons with destructive periodontitis. The masses of spirochetes characteristically synchronized their movement which produced rippling waves of motion.

In other fields we observed great numbers of thick flexing rods (2.5 x 5-15 microns) attached to the outer surfaces of the static mass or to the "brush patterns". The large flexing rods appeared so closely assembled that no spirochetes could be detected among them.

Only in this microbial complex were amoebae consistently observed. Numerous amoebae were often found in clustered positions around the gyrating ends of the spirochetes and flexing rods. It would appear that this ecological environment is favorable to amoebae.

Another predominant feature found in destructive periodontitis was the vast accumulation of white blood cells in the too-numerous-to count range. The white blood cells were located in the outer regions of the bacterial congregations, away from the highly turbulent spirochetal configurations that covered the dense masses of static forms. These findings suggest that white blood cells may be forced to locate in fluids that circulate between turbulent populations and the epithelial cells of pocket walls, i.e., far from surfaces coated with aggressive bacteria.

Management of Crevice Radical Infections: Data are now being prepared for computer analysis on about 150 cases that have been treated up to six years with monitored and modulated therapy (MMT) that uses conservative periodontal therapy for the elimination of specific disease-associated microorganisms. Preliminary results indicate that 1) Cases may go progressively downhill following surgical periodontics aimed at correction of morphological and anatomical features and modulated solely on the basis of macroscopic findings. In at least twelve cases of this type the disease has been arrested following correction of the bacterial defects by MMT. 2) The data also show that adequate correction of bacterial conditions in more serious lesions cannot be attained without a course of systemic antibiotics, e.g., tetracycline. 3) It has been possible to keep cooperative patients "free" of disease-associated bacteria and high counts of white blood cells for up to five years.

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

This microscopic study has provided evidence that examinations of crevicular plaque specimens provide far greater insight into the bacterial status of a case than "scores" of morphological and anatomical defects. Counts of white blood cells and disease-associated motile bacteria can be determined quickly by a chairside examination and thereby provide the clinician and patient with information that can be used to develop an appropriate therapeutic regimen and to modify the therapy as needed.

PROPOSED COURSE:

This project will terminate due to the retirement of Dr. Keyes.

PUBLICATIONS:

Keyes, P. H., Rogosa, M., Rams, T. E., and Sarfatti, D. E. 1981. Diagnosis of crevicular infections: Disease-associated bacterial patterns in periodontal lesions. In "Host-Bacterial Interactions in Periodontal Disease". S. Mergenhagen and R. Genco, eds. In Press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00208-05 LMI
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Genetic and Molecular Analysis of the Physiology and Pathogenesis of Oral Microorganisms		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT St. Martin, E. J. Senior Staff Fellow LMI NIDR		
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Microbiology Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md. 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Several metabolic systems in <u>Streptococcus mutans</u> were examined using genetic and molecular techniques. A second <u>transport</u> system for <u>glucose</u> was identified. Using <u>mutants</u> defective in glucose phosphotransferase activity (PTS), we were able to demonstrate that glucose transport and metabolism can occur in the absence of PTS activity. Analysis of this second glucose transport system using metabolic inhibitors revealed that it was driven by a <u>proton motive force</u> . The <u>genes</u> for <u>lactose</u> enzymes in <u>S. mutans</u> and <u>S. lactis</u> were examined by <u>heterologous transformation</u> into a lactose-negative recipient strain of <u>S. sanguis</u> . Analysis of transformants revealed that the genes that code for lactose PTS and phospho- β -galactosidase activity are located together on the chromosome in <u>S. mutans</u> but present on a <u>plasmid</u> in <u>S. lactis</u> .		

OBJECTIVES:

The general objectives of this research program are to use genetic and molecular techniques to examine the regulation and function of several, key metabolic reactions present in cariogenic microorganisms. More specifically, we have undertaken the study of sucrose, glucose and lactose utilization by S. mutans.

MAJOR FINDINGS:

1. Alternative mechanisms for glucose transport in S. mutans.

We have previously demonstrated that glucose can be transported into S. mutans by a phosphoenolpyruvate-dependent phosphotransferase system (PTS) and mutants that were missing this activity were isolated. The glucose PTS-negative mutants, however, are still capable of rapid growth on glucose and therefore, must possess a second glucose transport system. A study of this second transport system was initiated in collaboration with Dr. Ian R. Hamilton at the University of Manitoba. Using the PTS-negative mutant, it was now possible to examine the nature of this second glucose uptake system under continuous culture conditions. At saturating substrate levels, 99% of glucose uptake by the mutant was mediated by the non-PTS system. Uptake studies using these cells in the presence and absence of metabolic inhibitors revealed that the energy for this transport was not obtained from ATP but from a transmembrane proton gradient. The second (non-PTS) glucose transport system in S. mutans is, therefore, a proton motive force driven permease. The search for general inhibitors of sugar uptake in S. mutans must now take into account both transport systems.

2. Genetic and molecular characterization of lactose catabolic genes.

Most streptococci metabolize lactose by the same catabolic pathway. Lactose enters the cells by a phosphotransferase system (PTS) followed by cleavage of intracellular lactose phosphate by phospho- β -galactosidase (P- β -Gal). The genes for lactose utilization in S. mutans and S. sanguis are located on the bacterial chromosome, however, lactose utilization in S. lactis is associated with the presence of extrachromosomal plasmid DNA. Because lactose enzymes are easy to assay and possibly plasmid encoded, we have used the lactose genes as a model to develop a genetic exchange system that can be used with many species of streptococci. Mutants of S. sanguis that are missing one or both of the lactose enzymes were constructed from a strain that is competent for heterologous DNA genetic transformation. Purified S. mutans DNA and S. lactis plasmid DNA were capable of repairing both lactose specific genetic lesions in the recipient S. sanguis mutant. Molecular and enzymatic analysis of transformants revealed that both the lactose PTS and P- β -Gal genes were transferred from the S. lactis plasmid into the chromosome of S. sanguis. Transfer frequency analysis demonstrated that both genes are linked. In addition to permitting the transfer of streptococcal genes by heterologous transformation, the S. sanguis recipients can also be used to select for

cloned genes using recombinant DNA technology. In collaboration with Dr. Donald J. LeBlanc at the National Institute of Allergy and Infectious Diseases, a multicopy recombinant plasmid vector is currently being examined for possible lactose gene cloning into our recipients. Because we have previously demonstrated natural chromosomal and plasmid DNA exchange between these streptococci, our experiments do not fall under the NIH recombinant DNA guidelines.

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

The pathogenic potential of oral microorganisms resides in their ability to effectively colonize and proliferate on dental enamel and heart valve tissue surfaces. Once established on these sites, the production of large amounts of metabolic end-products from fermentative metabolism can lead to localized destruction of these sites. The use of genetic and molecular analysis techniques to examine the basic physiology and ecology of these bacteria will permit us to determine which of the many properties possessed by these microbes might be important for the expression of disease and suggest possible preventative measures.

PROPOSED COURSE OF STUDIES:

1. Genetic and molecular characterization of sucrose catabolic genes.

We have found that S. mutans has two metabolic strategies for utilizing sucrose. Sucrose either can be transported into the cells by a phosphotransferase system and the resulting sucrose 6-phosphate cleaved by an intracellular hydrolase or sucrose can be split outside the cells by a complex of different extracellular enzymes such as invertase and glucosyl- and fructosyl-transferases. Genetic and molecular manipulation of these enzyme systems will permit the design of effective sucrose transport analogs and allow the rapid purification of individual extracellular enzymes. In order to perform the genetic analysis of these genes, we will utilize a heterologous transformation system that was recently used to transfer lactose catabolic genes from S. mutans and S. lactis into mutants of a competent strain of S. sanguis. We are currently constructing similar mutants of S. sanguis that have specific lesions in all the enzymes of both sucrose pathways to serve as recipients for S. mutans and S. lactis sucrose genes. Because multiple pathways and enzymes are involved in sucrose utilization, the mutants must be constructed by a series of discrete mutational steps. We have recently isolated a sucrose-negative mutant of S. sanguis after five mutational steps. The recipient is competent for genetic transformation using heterologous S. mutans DNA and sucrose positive transformants are currently being examined. In addition to permitting the transfer of S. mutans genes by traditional transformation mechanisms, the recipients will also be used to select for cloned sucrose genes using recombinant DNA techniques.

2. The role of the sucrose transport system in the ecology and pathogenesis of S. mutans.

We previously described two metabolic strategies for sucrose utilization by S. mutans. Sucrose can be cleaved outside of the cell by low affinity enzymes (K_m , 3-12 mM) or transported into the cell by a high affinity (K_m , 0.07 mM) phosphotransferase system (PTS) followed by cleavage of intracellular sucrose 6-phosphate by a hydrolase. In order to determine what role the sucrose PTS pathway plays in the attachment, colonization and pathogenesis of S. mutans, we have initiated a collaborate study with Drs. Hans van de Hoeven and Henk de Jong at the University of Nijmegen in the Netherlands. Our laboratory has constructed and characterized a pair of S. mutans strains that have the same levels of extracellular enzymes but one of the pair has mutational lesions in both sucrose PTS and sucrose 6-phosphate hydrolase genes. The double mutant, thus, is very stable and will not revert during long term growth and animal studies. The pair also have different antibiotics resistance markers to permit rapid quantitation of individual strain numbers. These mutants will be used in both chemostat and gnotobiotic animal competition experiments to assess the role played by the sucrose PTS pathway in the survival and pathogenesis of S. mutans at both high (300mM) and low (1.0 mM) sucrose concentrations.

REFERENCE:

1. St. Martin, E. J., L. N. Lee and D. J. LeBlanc. 1981. Transformational analysis of a Streptococcus lactis lactose plasmid. Plasmid. 5: 229.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00273-03 LMI															
PERIOD COVERED October 1, 1980 - September 30, 1981																	
TITLE OF PROJECT (80 characters or less) Cell-Cell Interactions Between Oral Actinomycetes and Other Oral Bacteria																	
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 35%;">Kolenbrander, P. E.</td> <td style="width: 40%;">Senior Staff Fellow</td> <td style="width: 25%;">LMI NIDR</td> </tr> <tr> <td>Phucas, C. S.</td> <td>Microbiologist</td> <td>LMI NIDR</td> </tr> <tr> <td>Hurst-Calderone, S. L.</td> <td>Microbiologist</td> <td>LMI NIDR</td> </tr> <tr> <td>Cisar, J.</td> <td>Research Microbiologist</td> <td>LMI NIDR</td> </tr> <tr> <td>London, J. P.</td> <td>Research Microbiologist</td> <td>LMI NIDR</td> </tr> </table>			Kolenbrander, P. E.	Senior Staff Fellow	LMI NIDR	Phucas, C. S.	Microbiologist	LMI NIDR	Hurst-Calderone, S. L.	Microbiologist	LMI NIDR	Cisar, J.	Research Microbiologist	LMI NIDR	London, J. P.	Research Microbiologist	LMI NIDR
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Cisar, J.	Research Microbiologist	LMI NIDR															
London, J. P.	Research Microbiologist	LMI NIDR															
COOPERATING UNITS (if any) F. C. McIntire and A. Vatter, Univ. Colorado Med. Ctr., B. L. Williams, Univ. Washington Dental School, L. V. Holdeman, Virginia Polytechnic Institute & State Univ.																	
LAB/BRANCH Laboratory of Microbiology and Immunology																	
SECTION Microbiology Section																	
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md. 20205																	
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SUMMARY OF WORK (200 words or less - underline keywords) This project is designed to investigate the ecological importance of <u>coaggregation</u> between oral bacteria. These cell to cell interactions appear to be mediated by complementary surface components composed of a <u>lectin</u> on one cell type and a <u>carbohydrate</u> receptor on the other cell type. <u>Mutants</u> have been isolated and used to prove the <u>fimbrial structures</u> on the surface of <u>Actinomyces viscosus</u> T14V possess the <u>lactose-sensitive lectin</u> activity that mediates lactose-reversible coaggregation with <u>Streptococcus sanguis</u> 34. Mutants of <u>A. naeslundii</u> ATCC 12104 and of <u>S. sanguis</u> H1 have also been isolated and are being used to characterize other surface components involved in coaggregation. Lactose-reversible coaggregations between the gram-negative <u>Capnocytophaga ochracea</u> and <u>A. naeslundii</u> , <u>A. israelii</u> , or <u>S. sanguis</u> have been discovered which suggests that this type of coaggregation may be widespread among oral bacteria. Analysis of coaggregation between fresh human oral isolates of <u>S. sanguis</u> and <u>A. viscosus</u> or <u>A. naeslundii</u> obtained from the same site revealed that almost all isolates of these three species found in plaque are capable of coaggregation. Further study of interactions between oral bacteria is expected to provide a better understanding of the ecology of these <u>bacteria in the subgingival ecological niche.</u>																	

OBJECTIVES:

The establishment and persistence of bacterial microcommunities may be dependent on the interactions between different bacterial species that inhabit the microcommunity. Dental plaque represents one such microcommunity, which is characterized by a complex and highly organized set of interactions among oral bacteria as well as between bacteria and solid surfaces. It is likely that cell to cell interactions or co-aggregations are mediated by complementary cell surface components on the participating bacterial partners and the overall focus of this project is to investigate these surface components in an effort to understand the mechanism of coaggregation. This report presents the results of our investigations dealing with:

- 1) isolation and characterization of coaggregation-defective mutants of oral actinomycetes and streptococci;
- 2) specificity of coaggregation between oral cytophagas and other oral bacteria;
- 3) ecological study of interactions between human oral bacteria that are isolated from the same site.

METHODS EMPLOYED:

All techniques used are standard methods routine to the type of study conducted.

MAJOR FINDINGS:

Isolation and characterization of coaggregation-defective (COG⁻) mutants of oral actinomycetes and streptococci. Previous results from this laboratory suggested that the kinds of cell to cell interactions (co-aggregations) that occur between oral actinomycetes and streptococci are highly specific and are limited to five kinds. Each kind of coaggregation is mediated by a surface component on one cell type that is recognized by a complementary component on the surface of the other cell type. Although each kind of coaggregation is mediated by a single pair of complementary components, the participating cells possess other surface components that are involved in other kinds of coaggregations. To investigate each kind of coaggregation independently, a collection of appropriate mutants, each of which lacks a different surface component, would be invaluable. Mutants that are defective in their coaggregation properties (COG⁻) would be expected to be defective in a single kind of cell-surface component and would therefore, allow an independent analysis of each component involved in each kind of coaggregation. With this in mind, a selection technique was developed to isolate spontaneously occurring COG⁻ mutants of oral actinomycetes and streptococci. COG⁻ mutants of a desired actinomycete strain were obtained by mixing a population of cells of that strain with cells of an appropriate co-aggregating streptococcal strain. Cells of the actinomycete strain that did not coaggregate were collected in the supernatant fluid after differential centrifugation and subjected to two more cycles of coaggregation and differential centrifugation. After routine dilution plating and incubation, COG⁻ mutants were identified by their inability to coaggregate

with streptococcal strains that normally coaggregate in a specific pattern with the parent actinomycete strain. A variety of mutants of both actinomycetes and streptococci have been isolated by this technique. Of course, COG⁻ streptococcal strains were isolated and identified by their inability to coaggregate with appropriate actinomycete strains.

Of particular interest were the COG⁻ mutants of Actinomyces viscosus T14V and A. naeslundii ATCC 12104 that were unable to exhibit lactose-reversible coaggregation with certain streptococci. It is well known that the parent strains of both actinomycetes possess surface fimbriae (fibrils) and it was recently shown by Dr. John Cisar of the Humoral Immunity Section of this laboratory that isolated fimbriae from both strains mediate lactose-reversible agglutination with certain streptococci. Thus, the possibility that COG⁻ mutants were unable to participate in lactose-reversible coaggregations due to lack of fimbriae was investigated. By electron microscopy, the COG⁻ mutants of A. naeslundii ATCC 12104 were shown to lack fimbriae, whereas the COG⁻ mutants of A. viscosus T14V still possessed these structures. Thus, at least for A. naeslundii ATCC 12104, the loss of surface fimbriae correlates with the loss of the ability to participate in lactose-reversible coaggregation. The physical presence of fimbriae on the COG⁻ mutants of A. viscosus T14V suggested a second type of fimbriae on this strain not found on A. naeslundii ATCC 12104 and, in fact, two types of fimbriae have been isolated by Dr. Cisar from the parent strain of A. viscosus T14V.

A different method was used to prove that the second type of fimbriae found on the COG⁻ mutant of A. viscosus T14V was not involved in lactose-reversible coaggregation and that the missing fimbriae were the lactose-sensitive type. Monoclonal antibodies against each type of fimbriae were prepared by Dr. Cisar who showed that only one type contained the lactose-sensitive lectin activity. By using indirect immunofluorescence with the monoclonal antibodies, we have demonstrated that the parent strains of both actinomycetes possessed the lactose-sensitive fimbriae whereas the corresponding COG⁻ mutants did not. Also, the second type of fimbria was found on both the parent and COG⁻ mutant of A. viscosus T14V, but was undetectable on the parent or mutant of A. naeslundii ATCC 12104. Thus, the presence of two types of fimbriae on A. viscosus T14V and a single type on A. naeslundii ATCC 12104 was confirmed.

Specificity of coaggregation between oral cytophagas and other oral bacteria. Since most of the bacterial coaggregations studied to date involved the gram positive actinomycetes and streptococci, it was of interest to test the ability of certain gram negative bacteria to coaggregate with gram positive bacteria. The oral cytophagas are the only gram-negative oral bacteria that have been reported to adhere to tooth root powder and spheroidal hydroxyapatite. Earlier studies had shown that many of these isolates coaggregated only with a single A. israelii strain. Three closely related strains, Capnocytophaga ochracea, C. gingivalis, and C. sputigena have recently received a great deal of attention regarding their potential as oral pathogens. It was of interest to compare the coaggregation properties of these strains to those of the oral cytophagas studied previously.

All three Capnocytophaga strains coaggregated with five of the six A. israelii strains tested. None of these coaggregations was reversed by lactose which was like that found previously with the oral cytophagas and A. israelii. However, lactose-reversible coaggregation was observed in the mixture of C. ochracea and A. israelii CROB 2052. Although lactose-reversible coaggregations are common between Streptococcus sanguis and A. viscosus or A. naeslundii, they have rarely been observed with gram-negative bacteria. Further investigation with C. ochracea revealed lactose-reversible coaggregation with S. sanguis and A. naeslundii but not with A. viscosus. No coaggregation was seen between either of the other two Capnocytophaga spp. and S. sanguis but C. gingivalis exhibited weak lactose-nonreversible coaggregations with A. viscosus and A. naeslundii. Thus, Capnocytophaga spp. coaggregate with A. israelii like that found with the closely related oral cytophagas examined earlier. Perhaps the most significant observation from this study is the lactose-reversible coaggregations between C. ochracea and other oral bacteria. These results add to the growing body of evidence that oral bacteria often interact by means of a lactose-reversible coaggregation. The precise ecological significance of this fact, however, will require further study.

Ecological study of interactions between oral bacteria isolated from the same site. In an earlier study we examined fresh oral actinomycete and streptococcal isolates obtained from 16 individuals and demonstrated that the surface structures involved in coaggregation were similar or identical to those observed with stock culture strains. Each streptococcal isolate was tested for its ability to coaggregate with reagent actinomycete strains that represented the actinomycete coaggregation groups A and B. The same was done for fresh actinomycete isolates and reagent S. sanguis strains representing the four streptococcal coaggregation groups 1, 2, 3 and 4. One of the observations from that study was that about 40% of the S. sanguis isolates did not coaggregate with any of the reagent actinomycetes. In contrast, 100% of the A. viscosus isolates and more than 90% of the A. naeslundii isolates coaggregated with reagent S. sanguis strains.

An unresolved question, therefore, was why such a high percentage of fresh S. sanguis isolates failed to coaggregate. It should be noted that these fresh streptococcal isolates were not tested with the two new actinomycete coaggregation groups C and D that were described in the above study. To answer this question, a carefully controlled investigation of bacteria obtained from isolated sites was needed, because S. sanguis isolates that did not coaggregate with reagent actinomycetes may be able to coaggregate with appropriate actinomycetes (Group C or D) isolated from the same site. We examined fresh isolates of actinomycetes and streptococci that were selected from plaque samples taken from the same and different tooth surfaces from eight patients. These isolates were obtained from L. V. Holdeman and W. E. C. Moore at the Anaerobe Laboratory, VPI, Blacksburg, Va., during the course of their extensive study on bacteria isolated from subgingival and supragingival sites on specific tooth surfaces in patients with various forms of periodontal disease.

The results confirmed our earlier data in that all of the A. viscosus and A. naeslundii and about 60% of the S. sanguis isolates coaggregated with reagent strains. However, as seen before, 40% of the S. sanguis isolates failed to coaggregate with reagent actinomycetes of groups A and B. On testing these coaggregation negative streptococci with actinomycetes isolated from the same site, a strong coaggregation was observed only with actinomycetes that represented coaggregation group D. Further testing revealed that these streptococci coaggregated with reagent group D actinomycetes as well as group D actinomycetes freshly isolated from other patients. Taken together, the results of this study and our previous work indicate that:

- 1) nearly 100% of fresh human isolates of A. viscosus, A. naeslundii, and S. sanguis coaggregate.
- 2) Coaggregation among these three species is not a random event. All coaggregations can be explained by surface to surface interactions involving at least one but not more than five complementary structures.
- 3) Fresh isolates and reagent strains exhibit identical coaggregations.
- 4) Isolates of these three species from plaque possess surface structures that mediate coaggregation and bacteria that have lost these structures do not participate in plaque formation.

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

As more information is obtained about coaggregations between oral bacteria, it becomes increasingly evident that these cell to cell interactions are not random but rather are very specific in nature. The specificity of the interactions resides in complementary surface structures which can be studied independently with the aid of coaggregation defective mutants.

Characterization of these structures is expected to lead to a more comprehensive understanding of the mechanisms involved in cell to cell interactions and in attachment or adherence interactions between bacteria and solid surfaces. It is already evident that these cell to cell interactions are widespread among the oral bacteria and now include the oral cytophagocytobacteria which are prominent members of both the subgingival and supragingival bacterial populations. It is anticipated that a study of coaggregation among oral bacteria will provide insight into the sequential colonization of tooth surfaces by plaque bacteria and the temporal changes in bacterial populations observed in progressing states of periodontal disease.

PROPOSED COURSE:

My research efforts will be continued and expanded in two major distinct but closely related areas of coaggregation among oral bacteria. First, coaggregation-defective mutants of S. sanguis, A. viscosus, and A. naeslundii will be used to investigate the molecular mechanisms of lactose-reversible lectin-carbohydrate interactions. Mutants will be invaluable in this study because with them, the structures that mediate cell to cell interactions can be examined independently, and a complete

characterization of each surface structure can be accomplished. Second, well characterized oral isolates such as Fusobacterium sp. that are supplied by collaborators at Virginia Polytechnic Institute and State University will be used to examine coaggregation among other groups of oral bacteria. It is expected that coaggregations will be found among many different kinds of bacteria and that the additional information obtained about this very important form of cell to cell communication will enable us to understand ecological relationships between oral bacteria and their host.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00045-10 LMI
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Role of Macrophage, Keratinocyte, and Lymphocyte Mediators in Immunity		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Oppenheim, J. J. Dougherty, S. F. Carter, C. Stadler, B. Luger, T. Siraganian, R. P. Chou, Y. K. Farrar, J. J. Erikson, M. Sztein, M.	Medical Officer Biologist Microbiologist Visiting Fellow Guest Worker Medical Officer Visiting Fellow Research Microbiologist Guest Worker Visiting Fellow	LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any) B. Mathieson, NIAID, NIH; M. Mage, NCI, NIH; D. Sauder and S. Katz, NCI, NIH; D. Rosenstreich, Albert Einstein College of Medicine, New York, P. A. Murphy, Johns Hopkins Univ. School of Medicine, Baltimore, Md.		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Cellular Immunology Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md. 20205		
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CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Normal <u>monocytes</u> , <u>keratinocytes</u> and <u>lymphocytes</u> as well as cell lines when activated by <u>antigenic</u> or <u>polyclonal stimulants</u> produce a multiplicity of <u>immunoregulatory mediators</u> with potent biological effects on a wide variety of target cells at concentrations of 10^{-10} to 10^{-15} M. Activated macrophages produce <u>interleukin 1</u> (IL 1) which enhances the proliferation of peanut nonagglutinating (PNA) thymocytes and induces them to produce the <u>lymphokine IL 2</u> which in turn induces proliferation by PNA ⁺ thymocytes. The IL 1 has pleomorphic effects in that it stimulates <u>hepatocytes</u> to produce <u>serum amyloid A (SAA)</u> , is a growth factor for <u>fibroblasts</u> and has <u>endogenous pyrogenic activity</u> . The keratinocyte factor which is biochemically similar to IL 1, also augments lymphocyte and fibroblast proliferation, as well as IL 2 and SAA production. Murine <u>monoclonal anti human IL 2 antibodies</u> have been obtained which inhibit the T cell growth activity of IL 2 as well as lectin induced lymphocyte proliferation and B cell antibody production in response to antigens. <u>Immunoaffinity columns</u> prepared from these antibodies absorb supernatant IL 2 activity. Studies of these hormone-like factors and inhibitory antibodies will enable us to learn to manipulate immunological and <u>inflammatory reactions</u> .		

OBJECTIVES:

The regulation of production and role of mediators produced by human and murine monocytes, keratinocytes and lymphocytes that amplify immunological and inflammatory reactions is being investigated. These endogenous nonspecific factors are produced when these cells are activated by a wide variety of antigenic, polyclonal or injurious stimulants. The monocyte derived mediator is now called interleukin 1 (IL 1). IL 1 has a wide variety of biological effects including promoting thymocyte proliferation, increasing lymphocyte functions such as lymphokines and immunoglobulin production and also stimulating nonlymphoid cells that contribute to systemic inflammatory reactions. Thus IL 1 or a similar factor stimulates cells in the hypothalamic fever center and it may therefore be related to endogenous pyrogen. IL 1 stimulates "reticular" fibroblasts in the synovia of inflamed joints to produce inflammatory prostaglandins and collagenase and stimulates cultured fibroblasts to grow. IL 1 also appears to stimulate hepatocytes to produce acute phase proteins such as serum amyloid A (SAA). The lymphocyte mediator which is produced by the "helper-inducer" subpopulation of lymphocytes is called interleukin 2 (IL 2). It also has a variety of key biological effects on lymphocyte growth and functions including promoting the proliferation and maturation of the cytotoxic T lymphocyte (CTL) subpopulation. IL 2 indirectly also promotes B cell proliferation and immunoglobulin production. Thus both IL 1 and IL 2 are key endogenous amplifying signals which we are attempting to characterize biochemically and biologically. Understanding the mechanisms that control the production as well as the means by which these mediators exert their crucial effects in immunity and inflammation can potentially provide means of therapeutic manipulation of inflammatory reactions.

METHODS:

We are studying human IL 1 and IL 2 predominantly in tissue culture and at times assay their in vivo effects in animal models. The IL 1 is obtained from the buffy coat fractions of peripheral blood (purified by Ficoll-Hypaque centrifugation) kindly supplied us by the NIH Blood Bank or from the murine P388D1 macrophage cell line. The IL 2 is obtained either from the buffy coat of peripheral blood or from tonsillar or splenic tissues kindly supplied by the Pathology Dept. of Children's Hospital of Washington, D. C. or from a human T lymphocyte line. The cells are cultured for several days in large batches with the appropriate stimulants such as phytohemagglutinin (PHA), endotoxin (LPS), Concanavalin A (Con A) and/or phorbol myristate acetate (PMA), and the supernatant activity tested, concentrated and purified. The mediators are routinely bioassayed for their mitogenic effect on murine (C3H/HeJ) thymocytes, peripheral human T and B lymphocytes and on murine cytotoxic T lymphocyte lines (CTL). The effect of the mediators on thymocyte differentiation markers is being studied using fluorescence activated cell sorter (FACS) techniques. The capacity of these mediators to increase immunoglobulin and lymphokine production and promote nonlymphocytic cell functions is also being tested.

MAJOR FINDINGS:

1. The possible developmental effects of the interleukins have been studied in collaboration with Drs. B. Mathieson and M. Mage. The effects of these mediators on the proliferative response and phenotypic characteristics of thymocyte subpopulations were investigated using a fluorescence activated cell sorter. Only the subpopulation of thymocytes that is not agglutinated by peanut agglutinin (PNA) which corresponds with the immunocompetent medullary component of the thymus was able to proliferate in response to IL 1 and IL 2 in conjunction with lectins and to produce IL 2. In contrast 98% pure PNA⁺ (cortical subpopulation) thymocytes could not react to IL 1, nor produce IL 2, but could react only to IL 2 plus a lectin. Furthermore, when unfractionated thymocytes are cultured for 72 hrs with lectins with or without added IL 1 they show a reduction in PNA and LY 2 expression. These mitogenic stimulants thus induce some cultured thymocytes to change from a "cortical" to a "medullary" phenotype. This change is presumably mediated by IL 2 produced by "medullary" thymocytes acting on "cortical" thymocytes and may reflect a pathway of in vivo intracellular communication.

2. Dr. Marcelo Sztein has studied some of the effects of IL 1 on nonlymphocytic cells. He finds that intraperitoneal injection of partially purified human or mouse IL 1 results within 4-18 hrs in elevation of serum amyloid A (SAA) levels as determined by radioimmunoassays. Furthermore, both rabbit endogenous pyrogens with isoelectric points at pH 7.3 and pH 5 (EP 7 and EP 5, provided by Dr. P. A. Murphy) which are biochemically similar to IL 1 and also have thymocyte proliferative activity, when injected induce murine SAA. Both the SAA inducing and IL 1 activity of only the EP 7 but not the of the EP 5 moiety were inhibited by antibody to EP 7. These findings lead to the conclusion that IL 1 or a group of closely related monokine mediators are secreted by activated monocytes/macrophages that stimulate not only lymphocyte functions but also cells in the hypothalamic fever center and hepatocytes. Thus this monokine(s) not only augments immunological reactions but induces systemic responses to inflammatory and injurious stimuli.

3. In collaboration with Drs. D. Sauder and S. Katz the possibility that murine epidermal Langerhans cells which have some similarities to macrophages produce IL 1 was tested. Cultured fresh murine epidermal cells did produce a thymocyte activating factor (ETAF). However, selective depletion of the Langerhans cells did not block ETAF production. Furthermore, Dr. Thomas Luger concomitantly found that a murine keratinocyte cell line (PAM 212) also produced ETAF activity. This activity like IL 1 is about 15-20 K MW, is stable from pH 5.0-11.0, labile at 80°C, but unlike IL 1 yields only a single peak on isoelectrofocusing with a pI of 5.2. The biological activity of ETAF is identical with that of IL 1 in that it augments lectin induced thymocyte and lymphocyte proliferation, induces IL 2 production, activates in vitro fibroblast proliferation and in vivo SAA (acute phase protein) production. These observations suggest that epidermal cells also have the capacity to produce a "cytokine" that can mobilize inflammatory as well as immunological responses.

4) Dr. Beda Stadler has partially purified human IL 2 by sequential chromatography using phenyl sepharose, DEAE sephacel, AcA 54 gel filtration and isoelectrofocusing. This yields a single peak of 15,000 MW activity on AcA 54, which is electrophoretically heterogeneous on isoelectrofocusing with three peaks of activity having pI's of 6.5, 7.2 and 8.2.

5. In collaboration, with Dr. Reuben Siraganian monoclonal antibodies were prepared against the AcA 54 peak of IL 2 activity. BALB/c mice were immunized with the human IL 2 in complete Freund's adjuvant over a period of 2 months, and their spleen cells transferred into irradiated (500 r) BALB/c recipients that were simultaneously immunized with IL 2 intraperitoneally (IR). Four days after the adoptive transfer the spleen cells were hybridized with a BALB/c plasmacytoma line and the supernatants of cultured HAT resistant hybridoma cells were tested for their capacity to inhibit IL 2 dependent CT₆ cell line proliferation. Six inhibitory clones were selected and injected IP into BALB/c mice to obtain ascites fluid rich in inhibitory anti IL 2 of the μ or γ class. Immunoaffinity columns that were prepared using the most inhibitory anti IL 2 successfully absorbed IL 2 activity out of supernatants. The anti-IL 2 can completely inhibit the lymphoproliferative responses of human mononuclear cells in response to IL 2, as well as to the lectins PHA and Con A. The anti IL 2 also inhibited all 3 peaks of IL 2 obtained by IEF and cross-reacted to inhibit the lymphoproliferative effects of rat, and mouse IL 2 as well. Anti IL 2 also inhibited in vitro antibody responses by murine spleen cell cultures to antigens.

6. A similar approach has been used to produce murine monoclonal antibodies against the 50-70 K fraction of sephadex G200 chromatographed human IL 1. These antibodies partially inhibit the thymocyte proliferative response to IL 1, but do not block CT6 growth in response to IL 2. However, sepharose coupled anti IL 1 is only minimally effective in absorbing IL 1 activity suggesting that it is a low affinity antibody. Therefore better binding antibodies are being prepared by further purification of the ascites fluids and more prolonged sensitization of BALB/c prior to hybridization.

7. Dr. Beda Stadler has also investigated the effects of the interleukins on the lymphocyte cell cycle. These studies were performed using flow cytometry to establish increases in lymphocyte RNA content as they shift from G₀ to G₁ and thymidine incorporation as an indicator of S phase. These studies indicated that exogenous polyclonal stimulants such as PHA, Con A and PMA could shift peripheral lymphocytes from G₀ into G₁ phase of the cell cycle, and could induce lymphocytes to develop receptors for IL 2, but that IL 1 was required to induce IL 2 production. The IL 2 in turn was the required signal for induction of S phase and mitoses. In the process of performing these studies a human as well as mouse T lymphocyte line was found that could be stimulated by lectins and PMA to produce considerable IL 2 activity. Only those T cell lines whose G₁ phase was prolonged by these stimuli could be stimulated to produce IL 2. Thus IL 2 production was generally maximal prior to S phase.

8. Mark Erikson a predoctoral student from the University of Maryland is pursuing the investigation of the role of intracellular messengers in the function of lymphocyte subpopulations. We have previously observed that the human T γ lymphocyte subpopulation, which is enriched in suppressor cell activity, produces much more cAMP when stimulated with cAMP agonists than does the T μ subpopulation, which is enriched in helper activity. We have now used monoclonal antisera to obtain lymphocyte subpopulations with more clearly separated suppressor and helper roles. We will test the effect of modulating the cAMP levels of these subpopulations on their functional activities.

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

Periodontal inflammation is immunologically mediated and has been shown to involve both cellular and humoral host reactions to pathogenic micro-organisms. In the case of man, the contribution of host defense mechanisms to the inflammatory state can best be analyzed using tissue culture models. We have previously demonstrated that pathogenic oral organisms such as Actinomyces viscosus are potent in inducing in vitro IL 1 and lymphokine production. Thus monocyte as well as lymphocyte derived mediators presumably actively participate in oral inflammatory processes. For example, production of mediators by oral mucosal cells in normal and ulcerative diseases is being investigated. Since these mediators play an important role in augmenting inflammatory responses, and since they can be recovered from supernatants, they provide us with the opportunity of manipulating tangible regulatory factors that may modulate wound healing and inflammation including that which occurs in periodontal diseases.

PROPOSED COURSE:

We will continue to purify, isolate and identify the monocyte keratinocyte and lymphocyte derived immunoregulatory factors. This can be facilitated by the availability of monoclonal antibodies since this enables us to absorb and elute factors from immunoaffinity columns, which provides an excellent means of obtaining them in quantity with minimal contamination. These monoclonal anti-interleukins can also be used to develop radioimmunoassays for the detection and quantitation of the mediators and further to study the effects of inhibiting their functions in vitro and in vivo. The possibility that these mediators may also participate in normal development and differentiation and their effects on precursor cells as well as other target cells such as endothelial and smooth muscle cells will be studied. Finally, the intracellular effects of exogenous stimulants and endogenous mediators respectively must be studied to gain a greater understanding of the means by which these stimulants influence target cell functions.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00131-07 LMI																				
PERIOD COVERED October 1, 1980 through September 30, 1981																						
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NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Farrar, John J.</td> <td style="width: 33%;">Research Microbiologist</td> <td style="width: 15%;">LMI</td> <td style="width: 19%;">NIDR</td> </tr> <tr> <td>Hilfiker, Mary L.</td> <td>Post Doctoral Fellow</td> <td>LMI</td> <td>NIDR</td> </tr> <tr> <td>Farrar, William L.</td> <td>Microbiologist</td> <td>LMI</td> <td>NIDR</td> </tr> <tr> <td>Benjamin, William R.</td> <td>Post Doctoral Fellow</td> <td>LMI</td> <td>NIDR</td> </tr> <tr> <td>Fuller-Farrar, Janet</td> <td>Microbiologist</td> <td>LMI</td> <td>NIDR</td> </tr> </table>			Farrar, John J.	Research Microbiologist	LMI	NIDR	Hilfiker, Mary L.	Post Doctoral Fellow	LMI	NIDR	Farrar, William L.	Microbiologist	LMI	NIDR	Benjamin, William R.	Post Doctoral Fellow	LMI	NIDR	Fuller-Farrar, Janet	Microbiologist	LMI	NIDR
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LAB/BRANCH Laboratory of Microbiology and Immunology																						
SECTION Cellular Immunology Section																						
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, MD 20205																						
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:																				
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																						
SUMMARY OF WORK (200 words or less - underline keywords) Macrophage-mediated activation of <u>helper T cells</u> results in the production of a series of antigen-nonspecific factors which have dramatic immunoregulatory effects on target macrophages, B cells and T cells. We have utilized <u>phorbol myristic acetate</u> -stimulated EL-4 thymoma cells to study various aspects of the production and mechanism-of-action of one of these factors <u>Interleukin 2 (IL 2)</u> . Despite the fact that PMA induces the production of IL 2 in the EL-4 cells, the general rate of protein, RNA, and DNA synthesis of the cells is dramatically decreased. We have purified the EL-4-derived IL 2 to approximately 4,000,000 units of IL 2 per mg of protein and in the process shown the factor to be distinct from both <u>colony-stimulating factor</u> and <u>B cell growth factor</u> . Studies on the interaction between <u>IL 2 and its receptor</u> indicate that <u>receptor-mediated endocytosis</u> of IL 2 may be important in the mechanism of action of IL 2. Finally, absorption of IL 2 by specific receptors on suppressor T cells may represent one mechanism by which T cells can non-specifically <u>suppress immune responses</u> .																						

OBJECTIVES:

The principal objectives of this research project are 1) to purify and characterize the antigen nonspecific murine lymphokine Interleukin 2 (IL 2) and 2) to determine the mechanism-of-action of this soluble factor on the humoral and cell mediated immune responses.

METHODS:

Standard in vitro lymphocyte culture methods for the induction and assay of antibody and cell-mediated immune responses were utilized including the enumeration of antibody forming cells by the Jerne hemolytic plaque-forming cell (PFC) assay and the ⁵¹Cr release assay for quantitation of cytotoxic lymphocytes. Standard cell separation procedures were used to prepare purified preparations of B cells, T cells, and macrophages.

MAJOR FINDINGS:

On the production of IL 2 by phorbol ester-treated thymoma cells. We have examined the effect of phorbol esters on IL 2 production, proliferation, and DNA, RNA, and protein synthesis rates of EL-4 thymoma cells. We have found a correlation between an inhibition of proliferation and production of IL 2. The rates of DNA, RNA, and protein synthesis are also reduced by phorbol esters although IL 2 production is dependent on RNA and protein synthesis. Part of the mechanism of IL 2 production by phorbol esters may depend on a slowing of the cells through the G₁ phase of the cell cycle. It is not clear if phorbol esters enhance the synthesis of specific proteins (such as IL 2) during the general decline of protein synthesis or if phorbol esters act solely by slowing the transverse of the cell cycle allowing for accumulation of constitutively produced IL 2.

On the characterization and purification of thymoma-derived IL 2. We have examined the EL-4-derived IL 2 by SDS gel electrophoresis and found the monomeric molecular weight to be 21,000 as opposed to the estimate of 30,000 a determined by velocity sedimentation and gel filtration. Thus monomeric IL 2 is bound non-covalently to another macromolecule(s) totalling 10,000 in molecular weight. That IL 2 is a peptide was demonstrated in collaboration with Dr. Verner Paetkau in Edmonton, Canada who was able to translate EL-4-derived mRNA into biologically active IL 2 in xenopus oocytes.

We have utilized a multiple step purification scheme to purify IL 2. The procedure involves sequential ammonium sulfate precipitation, phenyl sepharose chromatography, tris glycine PAGE, and two dimensional electrophoresis (isoelectric focusing followed by SDS gel electrophoresis). With this procedure, we have purified IL 2 to approximately 4,000,000 units per mg protein with only one detectable contaminant. Experiments are currently in progress to more clearly resolve IL 2 from the contaminant.

On the resolution of IL 2 from other lymphokines. Because colony stimulating factor (CSF) or macrophage growth factor is capable of stimulating macrophages to produce IL 1 which can mimic IL 2 in certain biological assays, it is crucial to resolve CSF from IL 2. Through the use of hydrophobic chromatography on phenyl sepharose gels, we have separated CSF from IL 2 and shown that CSF which is devoid of IL 2 is not able to augment antibody response of stimulated nude mouse spleen cells.

Similarly, and in collaboration with Dr. Maureen Howard of NIAID, we have separated IL 2 (T cell growth factor) from B cell growth factor by SDS gel electrophoresis and selective absorption and elution of IL 2 from cytotoxic T cells (see below). These results are a pre-requisite to an analysis of the role of the two factors in the induction of primary antibody responses by immunized spleen cells.

On the interaction between IL 2 and its receptor. We have continued the studies begun last year of absorption of IL 2 by the factor-dependent cytotoxic T cell line, CT-6. Absorption of biological activity is used in these studies because purified, radiolabeled IL 2 is not yet available. We have shown absorption of IL 2 to be linearly proportional to cell number, to be target cell specific, to proceed in a time dependent measure at both 4°C and 37°C, and to be dependent on cellular energy. Recently we have shown that a 2-4 hr pulse of IL 2 is sufficient to cause proliferation of CT-6 cells 24 hours later. Methylamine, an inhibitor of receptor-mediated endocytosis, blocks the proliferative response to the 2-4 hr. pulse of IL 2. Furthermore, absorbed IL 2 can be eluted from the target cell with pH2 glycine buffer at 4°C but much less is eluted from cells incubated at 37°C. Methylamine increases the amount of IL 2 which can be eluted at 37°C. Therefore, IL 2 is apparently internalized by its target cell and this internalization process is probably necessary for the proliferative response of the cells.

On the absorption of IL 2 as a mechanism of non-specific T cell mediated immune suppression. Con A-treated lymphocytes nonspecifically suppress a variety of immune reactions. The mechanism of Con A-induced suppressor cells is not known; however, these lymphocytes have been reported to selectively absorb IL 2, a soluble mediator involved in numerous immune responses. We have therefore been examining whether competitive removal of IL 2 may be one mechanism by which cells suppress immune reactions. Con A-induced suppressor cells inhibited the *in vitro* plaque forming cell (PFC) response of mouse spleen cells in a dose-dependent manner. Maximal suppression occurred by the addition of 125,000 cells (5% final concentration). This suppression was blocked by the additional IL 2-containing supernatant at the time of suppressor cell addition. In order to further characterize this proposed mechanism of suppressor cell action, a cloned syngeneic IL 2-dependent T cell line (CT 6) was examined for suppressive activity. This cell line non-specifically suppressed the PFC response against SRBC and HRBC in a dose-dependent fashion and in addition readily removed IL 2 from culture supernatants. Addition of as few as 2500 cells (0.1% final concentration) resulted in significant suppression. This

inhibition was not due to a shift in the kinetics of the response, was not blocked by indomethacin and no inhibitory factors were detected in culture supernatants. Addition of IL 2-containing supernatant prevented the suppression induced by CT 6 cells. Suppression of the PFC response occurred only when CT 6 was added during the first 48 h of the 5 day response.

The results from these studies 1) further support the critical role of IL 2 in humoral immune responses, 2) suggest that suppressor cells and other proliferating T lymphocytes modulate immune responses by competitively utilizing IL 2, 3) suggest that IL 2 is important during the early stages of cellular interactions which subsequently lead to the PFC response. Current studies are further examining the role of soluble mediators or negative and positive regulation of immune reactions.

Significance to Biomed. Periodontal disease is characterized by an inflammatory response which is regulated by a complex network which includes antigen, antibody, complement, macrophages, helper and suppressor T cells and B cells as active components. These components serve to control the initiation, expression, maintenance and suppression of the inflammatory response and, hence, periodontal disease. Maintenance of this complex regulatory network is achieved by interactions between the participating cells; interactions which are mediated, in part, by soluble factors produced by the cells. The elucidation of the mechanism of action of the soluble factors, one of which is IL 2, is crucial to our understanding of inflammation.

PROPOSED COURSE:

In the coming year, we shall continue our efforts to purify EL-4-derived IL 2 and B cell growth factor and to examine the relative roles of each of these factors in the antibody response. Preliminary studies on the preparation of a radiolabelled preparation of IL 2 have begun and shall continue in an effort to further elucidate the mechanism by which IL 2 activates its target cells subsequent to interaction with the receptor.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00238-04 LMI
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Regulation of Macrophage Functions in Inflammatory and Immune Responses		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Steeg, P. S. Moore, R. N. Mergenhausen, S. E. Oppenheim, J. J. Farrar, J. J. Hilfiker, M. L.	Microbiologist Staff Fellow Chief, LMI Medical Director Research Microbiologist Postdoctoral Fellow	LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any) Stefanie N. Vogel, Asst. Professor of Microbiology, USUHS, Bethesda, Md.		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Cellular Immunology Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md.		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
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SUMMARY OF WORK (200 words or less - underline keywords) Several mechanisms regulating macro- <u>phage functions</u> in both inflammatory and immune responses have been elucidated. The <u>biology</u> and <u>biochemistry</u> of the <u>colony stimulating factors</u> (CSF) a group of immunomodulatory mediators have been studied. Methods have been developed for the <u>production and partial purification</u> of T-lymphocyte derived CSF. Serum-free super- natants of a stimulated cell line, when chromatographed in sequence by hydrophobic, ion exchange and lectin affinity chromatography yielded material with a <u>specific</u> <u>activity of >10 units/mg protein</u> . The <u>mechanism</u> by which CSF modulates macro- phage responsiveness to <u>bacterial endotoxin</u> was found to involve an <u>intermediary</u> <u>interferon priming stage</u> . Macrophage <u>initiation</u> of antigen-specific immune respon- <u>ses</u> is dependent on cell surface expression of Ia antigens. <u>Supernatants of lectin</u> <u>activated spleen cells (Con A sup)</u> have been found to <u>induce Ia macrophages to</u> <u>express Ia antigens</u> . <u>Biochemical characterization</u> of the Con A sup indicates that the active mediator is <u>immune interferon</u> . Conversely two mechanisms have been found that induce or maintain the Ia ⁺ state. Supernatant incubated Ia ⁺ macrophages subsequently incubated in supernatant-free medium become Ia ⁻ . Also, <u>bacterial en-</u> <u>dotoxin</u> inhibits Con A sup induction of macrophage Ia antigen expression.		

OBJECTIVE:

The objective of this project is to investigate regulatory mechanisms in inflammatory and immune responses which modulate macrophage functions.

MAJOR FINDINGS:

The regulation of macrophage function in inflammatory responses has been examined, particularly with respect to the roles of microbial products and two mediators, colony stimulating factors (CSF) and interferon (IFN). It has been demonstrated that CSF directly stimulates macrophages to produce lymphocyte activating factor, an immunostimulatory molecule. Moreover, CSF has been found to enhance macrophage responsiveness to other stimuli-macrophages treated with CSF subsequently exhibited enhanced responsiveness to bacterial endotoxin as manifested by increased IFN and tumor necrosis factor production.

In order to substantiate the aforementioned conclusions we have developed a protocol to produce large quantities of T-cell derived CSF under serum-free conditions. A subline of the murine thymoma cell line EL4, when stimulated with phorbol myristate acetate (PMA) produces CSF which appear to be biochemically and functionally indistinguishable from that produced by mitogen stimulated mouse spleen cells.

Techniques have been developed to separate EL4 cell-derived CSF and Interleukin 2 (IL 2). Although these mediators have similar molecular weights and charge characteristics, hydrophobic chromatography using phenyl sepharose effects a complete separation of these mediators.

Phenyl sepharose chromatography has been incorporated into a preliminary purification procedure for T-cell derived CSF. Preliminary experiments indicate that EL4-derived CSF, precipitated with ammonium sulfate and chromatographed in sequence on phenyl sepharose, DEAE sephacel and Con A sepharose yields a material with a specific activity of $> 10^7$ U/mg protein.

The mechanism of CSF enhancement of macrophage responsiveness to endotoxin has been investigated, using macrophage production of IFN as a model system. It has been found that incubation of macrophages with CSF resulted in the immediate production of a small amount (3 U/ml) of IFN, and it was therefore hypothesized that endogenously produced IFN may "prime" the macrophage culture for enhanced responsiveness to endotoxin. Experiments supporting this hypothesis are described as follows: (1) Incubation of macrophage cultures with L cell-derived CSF and anti-mouse fibroblast IFN antiserum abrogated the enhancing effect of CSF in cultures challenged with endotoxin; (2) this effect is not limited to L-cell derived CSF, as partially purified EL4-derived CSF also primes macrophages for enhanced IFN production; and (3) the enhancing effect of CSF is not limited to endotoxin as a second signal as both lymphokine and cytokine CSF preparations also enhanced IFN production in response to poly I: poly C. Conversely, pretreatment with anti-IFN antiserum abrogates these responses. We conclude that CSF stimulates at least some of the macrophages to produce IFN, and that IFN may mediate the enhancing effects of CSF.

This laboratory has also studied the cellular interactions which regulate macrophage function in immune responses. The antigen-specific immunological activation of T lymphocytes to participate in antibody production, cytotoxic T lymphocyte activation etc. has been shown to require the participation of macrophages or other accessory cells bearing I region associated (Ia) antigen membrane determinants. However, not all macrophages express Ia antigens and the mechanisms regulating macrophage Ia antigen expression have been unknown. We have investigated the hypothesis that T lymphocytes can influence macrophage Ia antigen expression, and have found that a supernatant of mitogen stimulated spleen cell cultures induced Ia⁻ peritoneal exudate macrophages to express Ia antigen. Summaries of our work with this project in the last year are as follows:

1. An improved assay system for lymphokine induction of macrophage Ia antigen expression was developed. The Ia⁻ murine macrophage cell line P388D₁, when cultured with the mitogen stimulated spleen cell supernatant (Con A Sup) expressed endogenous Ia antigen as detected by antiserum and complement mediated cytotoxicity.

2. Biochemical characterization of the active Con A sup mediator has been undertaken, and results to date indicate that this mediator is immune interferon (γ IFN). The active factor was found to be pH 2 and 3 sensitive, and resistant to heating at either 37 or 56°C for 1 hr. It has an apparent molecular weight of 35,000 on gel filtration, and on hydrophobic chromatography binds reversibly to phenyl sepharose. IFN activity, as measured by a Vesicular Stomatitis Virus plaque reduction assay coeluted with the Ia antigen inducing activity in each of these experiments. Both the active Con A sup mediator and IFN bind reversibly to poly-uridylic acid sepharose, an affinity column for IFN. Additionally, anti-murine γ IFN antibody, provided by Dr. H. Johnson (The University of Texas Medical Branch, Galveston, Texas), abrogated Con A sup induction of P388D₁ macrophage Ia antigen expression. Induction of macrophage Ia antigen expression is an extremely sensitive measure of IFN activity, requiring > 1U/ml IFN for maximal activity. We tentatively conclude that γ IFN induces Ia⁻ macrophages to express Ia antigen. Our results may explain in part previous reports demonstrating in vivo immunoenhancing effects of administration of small doses of IFN.

In parallel studies the differentiative effect of γ IFN on C3H/HeJ macrophage Fc receptor expression has been demonstrated. Unlike C3H/HeN mice, the Fc receptor expression of C3H/HeJ peritoneal exudate macrophages declines with time in culture; this decline can be prevented by incubation with the supernatant of lectin activated spleen cells (Con A sup). Using sequential ammonium sulfate precipitation and hydrophobic chromatography and isoelectric focusing the active Con A sup mediator was identified as γ IFN.

3. We have additionally asked how the loss of Ia antigen expression by macrophages is regulated. We have found that Con A sup cultured (Ia⁺) macrophages, subsequently cultured in supernatant-free medium⁺ become Ia⁻. Thus in the absence of the active Con A sup mediator Ia⁺ macrophages become Ia⁻.

4. Preliminary experiments suggest that other signals may also influence macrophage Ia antigen expression. Incubation of P388D₁-macrophages with Con A sup and bacterial endotoxin resulted in Ia⁺ cultures, suggesting that endotoxin can block Con A sup induction of macrophage Ia antigen expression.

SIGNIFICANCE TO BIOMEDICAL RESEARCH:

Macrophages occupy a central role in virtually all immune and inflammatory responses. Besides ingesting and killing microbial organisms these cells also function to activate T lymphocytes and to secrete a variety of substance which have profound effects on surrounding tissues and other cells of the immune system. These secretory products can either augment host defenses and repair processes or under certain circumstances promote tissue destruction. The experiments described above represent attempts to ascertain regulatory mechanisms functioning to control macrophage activities. The findings can be divided into two major categories. First, the colony-stimulating factors, which are produced by a variety of cell types involved in immunological and inflammatory responses, serve to augment a variety of immunologically nonspecific macrophage functions. These factors which have classically been known as myelopoietins were found not only to enhance macrophage responses to bacterial endotoxin but also to directly stimulate secretion of active molecules by macrophages. Colony-stimulating factors, therefore, appear to play dual physiological roles functioning both to increase the macrophage/granulocyte population and to stimulate macrophage secretory functions. Under normal circumstances CSF may, therefore, function to enhance both host defense and repair processes. However, under conditions of antigen persistence or autoimmune diseases, CSF and secondary macrophage products may promote the destructive activities associated with chronic inflammation. Second, genetically restricted functions of macrophages expressed through the phenotypically Ia⁺ macrophage subpopulation appear to be regulated by products of stimulated lymphocytes. These products may, therefore, be important factors in regulating the development of specific immune responses. A thorough understanding of these different molecular regulators of macrophage functions should provide a sound basis for manipulations designed to augment or depress selected aspects of the host's immune system.

PROPOSED COURSE:

Due to the departure of Dr. Moore effective 4/81 further investigation into the biology and biochemistry of CSF is no longer being pursued in this laboratory.

With regard to our studies examining the regulation of macrophage Ia antigen expression several lines of investigation are proposed:

1. Completion of the biochemical characterization of the Con A sup.
2. Further investigation of the functional significance of lymphokine modulated macrophage Ia antigen expression. Initial experiments indicate that Con A sup incubated peritoneal exudate macrophages provided accessory

cell function in the stimulation of the mixed leukocyte reaction significantly better than control supernatant incubated cells. Additional experiments are planned to investigate this question in an antigen specific system.

3. Further investigation of the effects of bacterial endotoxin on the regulation of macrophage Ia antigen expression. Our preliminary experiments, which demonstrate that endotoxin inhibits Con A sup induction of macrophage Ia antigen expression, suggest that a negative feedback signal may exist in this system. Moreover, these experiments may delineate a novel mechanism whereby bacteria can evade the host's immune system.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00242-04 LMI
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) The Role of Oxygen Radicals In Inflammation		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Hoffeld, J. T. Metzger, Z. Collison, B. C. Pick, E. Oppenheim, J. J.	Dental Officer Visiting Fellow Health Services Officer (COSTEP) Visiting Scientist Medical Officer	LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any) Richard D. deShazo, WRAMC, Washington, D. C.		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Cellular Immunology Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md. 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
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SUMMARY OF WORK (200 words or less - underline keywords) We have further defined the involve- ment of activated <u>macrophage-derived oxygen radicals</u> in <u>inflammation</u> . We have found that killed cells of <u>Actinomyces viscosus</u> , a prevalent organism in adult dental plaque, can induce the activation of macrophages, <u>in vivo</u> . These activa- ted macrophages can suppress lymphocyte proliferation, <u>in vitro</u> . The <u>suppression</u> was due to a combined effect of <u>oxygen radicals</u> and <u>cyclooxygenase products</u> . Since <u>granuloma</u> formation is one form of chronic inflammation, we studied the relationship of granuloma-inducing agents to macrophage activation. Killed <u>bacterial cells</u> or particles of <u>silica</u> , <u>bentonite</u> or <u>talc</u> inhibited spleen cell activities, <u>in vitro</u> , and this inhibition was reversible by enhancement of anti- oxidant capacity of the cultures. Since another property of chronic inflammation is depression of fibroblastic repair, we examined the action of activated macro- phages on <u>fibroblast</u> growth. Activated macrophages suppressed fibroblast pro- liferation by a combined effect of hydrogen peroxide and cyclooxygenase products. Further definition of the role of oxygen radicals in chronic inflammation should identify means of modulating both the tissue destructive and immune response components.		

MAJOR FINDINGS:

Histological and pathological examinations of chronic inflammatory sites, such as those present in periodontal disease, have shown not only that the cellular infiltrate deals inadequately with the noxious stimuli present (e.g., endotoxin from dental plaque bacteria), but also that the inflammatory cells may contribute to the tissue damage. Since one of the potentially immunosuppressive and tissue-destructive processes of which macrophages are capable is the production of oxygen radicals, we are studying the role of oxygen radicals in those processes. We have expanded our earlier finding in the areas described below.

The induction of activated macrophages, in vivo, by intraperitoneal injection of formalinkilled Corynebacterium parvum cells was found to be a generalized property of certain killed bacterial cells. Specifically, killed cells of the species Actinomyces viscosus, a prevalent organism in adult dental plaque, activated macrophages, in vivo. These activated macrophages could suppress mitogen-induced lymphocyte proliferation in a dose-dependent manner, and that suppression was reversible by a combination of catalase and indomethacin. These data implicate hydrogen peroxide and one or more products of the cyclooxygenase pathway as the effectors of the suppression.

In Hodgkin's disease, a lymphoma of humans, the proliferation of lectin-stimulated peripheral blood lymphocytes is severely depressed. In collaboration with Dr. R. D. deShazo, we have found that this suppression is attributable to macrophages in the responding cell population; furthermore, this suppression was partially reversed by the addition of both oxygen radical scavengers and indomethacin. These data again implicate oxygen radicals and one or more products of the cyclooxygenase pathway as the effectors of the suppression.

Since many of the products of the cyclooxygenase pathway have been shown to modulate cyclic nucleotide metabolism, we investigated the role of these regulatory molecules in the regulation of macrophage activation as measured by chemiluminescence. Chemiluminescence is one measure of the production of oxygen radicals by macrophages. We found that elevation of macrophage cyclic AMP had little effect on the production of oxygen radicals by pre-activated macrophages. In contrast, elevation of cAMP concentrations in resting macrophages prevented their progression to a state of activation capable of producing oxygen radicals. These data suggest that at a chronic inflammatory site, highly activated macrophages which release various cyclooxygenase products, may thereby block the activation of nearby non-activated macrophages.

As mentioned above, macrophages can be activated in vivo by administration of poorly degradable bacterial cells. These bacterial cells, or any of a broad array of undegradable mineral particles produce what is known as "low-turnover" granulomata, in vivo. This type of granuloma is characterized by poor resolution and depressed proliferation of lymphocytes. We tested each of these particles for its capacity to activate resting macrophages in vitro. C. parvum cells or particles of silica, bentonite or talc were all capable of inducing suppression of antigen- or mitogen-induced spleen cell activities. This suppression was due to peroxidative

processes as evidenced by the reversal of suppression by antioxidants such as α -tocopherol or 2-mercaptoethanol. The time course for the induction of suppression by particles paralleled that seen for the induction of activation of macrophages by spleen cell supernatants or bacterial endotoxin.

Since "low-turnover" granulomata are also characterized by impaired fibrosis we tested the hypothesis that activated macrophages may also alter fibroblastic repair processes. Indeed, we found that macrophages activated either in vivo or in vitro were capable of inhibiting the proliferation of fibroblasts. The reversal of this suppression by catalase and indomethacin again implicated hydrogen peroxide and one or more products of the cyclooxygenase pathway as mediators of the suppression of fibroblastic repair processes.

Thus, the activated macrophage appears to play a key role in controlling the resolution of a chronic inflammatory site. The oxidative metabolic activities of the macrophage, particularly the activities of the oxygen-radical-generating NADPH oxidase and the prostaglandin/thromboxane-generating NADPH oxidase and the prostaglandin/thromboxane-generating cyclooxygenase, appear to be the major regulators at chronic inflammatory sites.

OBJECTIVES:

- 1) Demonstrate both the deleterious and regulatory effects on mammalian cells of spontaneously generated oxygen radicals.
- 2) Define the regulatory interactions of the macrophage products: oxygen radicals, prostaglandins and reduced sulfhydryls.
- 3) Define both effective stimulants for the production of and scavengers against the effects of oxygen radicals.
- 4) Modulate the deleterious and regulatory effects of oxygen radicals by the use of stimulants and scavengers.
- 5) Apply these same research objectives to the study of chronic inflammation such as periodontal disease.

METHODS EMPLOYED:

- 1) In vitro model systems.
 - a) Primary antibody response of murine spleen cells to erythrocyte antigens.
 - b) Mitogen-induced proliferation of murine spleen cells.
 - c) Monolayers of murine peritoneal exudate cells grown in scintillation vials for chemiluminescence determination.

- d) Monolayers or suspensions of murine spleen cells or peritoneal exudate cells grown in microtiter plates for superoxide or hydrogen peroxide determination.
- 2) Assay for primary antibody response: Direct (IgM) plaque-forming cells measured by complement-mediated, antibody-dependent hemolytic assay.
- 3) Assay for lymphocyte proliferation: cultured cells pulsed with tritiated thymidine; cultured for an additional period; radioactivity measured on a scintillation counter.
- 4) Assay for prostaglandins: radioimmunoassay specific for class E prostaglandins
- 5) Assay for oxygen radicals:
 - a) Nonspecific: Cells were cultured in scintillation vials; when the chemiluminescence enhancer, luminol, is present, stimulated or non-stimulated oxygen radical production can be measured on a scintillation counter.
 - b) Hydrogen peroxide-specific: Horseradish peroxidase-dependent oxidation of phenol red was monitored by A_{600} of cell cultures on an ELISA plate scanner.
 - c) Superoxide-specific: Reduction of cytochrome c in the presence or absence of superoxide dismutase was monitored by A_{550} of cell cultures on an ELISA plate scanner.

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

The interactions of responding immune cells with each other or with neighboring cell types have been shown to involve a number of relatively long-lived, isolable mediators (e.g., lymphokines, monokines, stable prostaglandins). The involvement of relatively short-lived mediators (e.g., oxygen radicals, thromboxanes, prostaglandin endoperoxides, prostacyclin) has only recently become apparent. Oxygen radicals have been implicated in such in vivo conditions as rheumatoid arthritis and hyperuricemic arthritis as well as in vitro models of killing by immune cells. These mediators not only can affect surrounding cell types, but also can modulate the activity of other responding cells. Thus, an understanding of the mechanisms whereby oxygen radicals interact with various cells hold the promise of modulation of both immune reactivity and tissue damage in chronic inflammatory conditions such as granulomata and periodontal disease.

PROPOSED COURSE:

We propose to continue these studies in several different ways:

- 1) Using the hydrogen peroxide, superoxide, chemiluminescence and oxygen polarographic assays we will investigate the mechanisms of macrophage activation and its modulation by a number of pharmacological and biological agents.

- 2) Using the non-protein sulfhydryl and oxygen polarographic assays, we will examine the role of macrophage-derived reducing agents in the protection and stimulation of lymphocytes.
- 3) Using inbred strains of mice responsive and non-responsive to stimulation by oxidizing agents, we will examine the proliferogenic role of oxidative processes.
- 4) Using the murine footpad granuloma model of chronic inflammation, we will further examine the role of oxygen radicals in chronic inflammation.

PUBLICATIONS:

1. Hoffeld, J. T. 1981. Agents which block membrane lipid peroxidation enhance mouse spleen cell immune activities, in vitro: Relationship to the enhancing activity of 2-mercaptoethanol. European Journal of Immunology 11: 371-376.
2. Hoffeld, J. T., Metzger, Z., and Oppenheim, J. J. 1981. Oxygen-derived metabolites as inhibitors of immune responses, in vitro. In: Lymphokines, volume 2. E. Pick (editor). Academic Press, New York, pp. 63-66.
3. Metzger, Z., Hoffeld, J. T. and Oppenheim, J. J. 1981. Regulation by PGE₂ of the production of oxygen intermediates by LPS-activated macrophages. Journal of Immunology (in press).
4. Hoffeld, J. T. 1981. Oxygen radicals in inflammation and immunity. In: Host Bacterial Interactions in Periodontal Disease. R. J. Genco and S. E. Mergenhagen (editors). American Society of Microbiology. Washington, D. C. (in press).
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6. Hoffeld, J. T., Metzger, Z. and Oppenheim, J. J. 1981. Role of activated macrophage superoxide anions and hydrogen peroxide in immune suppression. In: Immunomodulation by Bacteria and Their Products. H. Friedman (editor). University Park Press. Baltimore, Maryland. (in press).
7. Metzger, Z., Moore, R. N., Hoffeld, J. T. and Oppenheim, J. J. 1981. A fibroblast derived factor activates macrophages to produce hydrogen peroxide in vitro. In: Heterogeneity of Mononuclear Phagocytes. O. Forster (editor). Academic Press. London. (in press).

8. Moore, R. N., Hoffeld, J. T., Farrar, J. J., Mergenhagen, S. E., Oppenheim, J. J. and Shadduck, R. K. 1981. Role of colony-stimulating factors as primary regulators of macrophage functions. In: Lymphokines, volume 3. E. Pick (editor). Academic Press, New York, pp. 119-148.
9. deShazo, R. D., Ewel, C., Londono, S., Metzger, Z., Hoffeld, J. T. and Oppenheim, J. J. 1981. Evidence for the involvement of monocyte-derived toxic oxygen metabolites in the lymphocyte dysfunction of Hodgkin's disease. *Clinical and Experimental Immunology*, 46 (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00261-03 LMI
PERIOD COVERED October 1, 1980 through September 30, 1981		
TITLE OF PROJECT (80 characters or less) Signal Requirements for Lymphocyte Activation.		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Weinblatt, Anita Corman Oppenheim, Joost J. Jenkins, Mark	Post Doctoral Fellow Medical Director Bio Lab Technician	LMI LMI LMI
		NIDR NIDR NIDR
COOPERATING UNITS (if any) David L. Rosenstreich, Albert Einstein College of Medicine, New York, N.Y.		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Cellular Immunology Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, MD 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) We have continued our study of signals involved in T cell activation. We have shown that <u>guinea pig</u> (GP) peritoneal exudate lymphocytes (PELS) when pulsed with antigen, release a T cell growth factor, <u>TSF</u> (<u>T cell stimulatory factor</u>). TSF induces the proliferation of purified guinea pig T cells in the presence of PMA, PHA, or Con A. The factor is rapidly produced, since significant activity is detectable after only 2 hours; activity is maximal by 18 hours and is still present at a 1/16 dilution. Since PHA and Con A can replace PMA as a comitogen for TSF, PMA is not unique. GP PELs are better producers of TSF than lymph node lymphocytes. Several lines of evidence suggest that TSF is the guinea pig equivalent of <u>TCGF</u> (<u>IL-2</u>). TSF containing supernatants have IL-2 activity when tested on the IL-2 requiring CT-6 cell line. When TSF containing supernatants were absorbed with CT-6 cells, there was a significant decrease of both TSF activity as well as IL 2 activity. Finally, purified human and mouse IL 2 have TSF activity while the macrophage product <u>IL 1</u> has no TSF activity. We are in the process of biochemically characterizing and purifying guinea pig TSF to enable us to study the role of TSF in inducing the biochemical and cell surface alterations that occur in lymphocyte activation.		

OBJECTIVES:

To understand the molecular signals required to activate T lymphocytes.

MAJOR FINDINGS:

In our previous progress reports we have described how the synthetic compound phorbol myristic acetate (PMA) was able to substitute for macrophages as a source of one of the activating signals in the mitogenic action of highly purified guinea pig T lymphocytes. In addition, we reported that peritoneal exudate lymphocytes (PELS) from immunized guinea pigs release a T-cell growth factor, TSF (T-cell stimulatory factor), when pulsed with antigen. TSF induces the proliferation of purified guinea pig T cells, but only in the presence of PMA, PHA, or Con A. Thus, TSF is an activating signal for lymphocytes and we have further characterized the nature of the TSF activity.

TSF is produced rapidly. Significant activity was detected within two hours and was maximal by 18-24 hours. Activity decreased but was still present by 48 hours. PELS produced relatively large amounts of TSF. Significant activity was detected at a $1/16$ dilution and was maximal at a dilution of $1/2$.

We previously reported that production of the factor is antigen specific, since generation of the activity requires that PELS be pulsed with an antigen to which the donor guinea pig has been primed. The effect of the factor is antigen non-specific, in that active supernatants are mitogenic for PMA treated non-immune as well as immune T cells. We also have shown that there is no genetic restriction in the effect of TSF. TSF generated by antigen pulsed strain 13 PELS is active on T cells from both strain 2 and strain 13 guinea pigs.

We have demonstrated that PMA is not unique and that PHA or Con A can replace PMA as a comitogen for TSF. Neither the lectins nor PMA nor endogenous TSF by itself is mitogenic for macrophage depleted T cells, yet any combination of two is stimulatory, suggesting that one signal modifies the cells so that they can respond to the other signal.

Several lines of evidence suggest that TSF is the guinea pig equivalent of TCGF (T cell growth factor), also known as interleukin 2 (IL 2). TSF containing supernatants are able to support the proliferation of the IL-2-dependent murine CT-6 cell line. CT-6 cells which are known to absorb IL-2 activity from IL-2 containing preparations are also able to absorb TSF activity. Absorption of TSF containing supernatants with CT-6 cells removes both TSF activity as assessed on guinea pig T cells as well as IL-2 activity as assessed in a standard IL-2 assay with CT-6 cells. We also tested the ability of other purified mitogenic factors to replace TSF. Highly purified mouse and human IL 2 have TSF activity while the macrophage product IL-1 (both mouse and human) has no TSF activity.

SIGNIFICANCE TO BIOMEDICAL RESEARCH:

The process of T cell activation is fundamental to almost all immune reactions. In order to more fully understand the immune process it is important to identify and characterize these factors. This will aid in the development of pharmacological agents which can specifically modulate immunity in certain disease states. TSF when purified and used in combination with PMA or other comitogens will not only expand our knowledge of lymphokines but also facilitate studies on the biochemical alterations involved in lymphocyte activation.

PROPOSED COURSE:

We plan to pursue the especially interesting observation that neither the lectins nor PMA nor endogenous TSF by itself is mitogenic for macrophage depleted T cells, yet any combination of the two is stimulatory. This suggests that one signal modifies the cells so they can respond to the other signal. In preliminary experiments we have shown that purified T cells pulsed for one hour with PMA will still proliferate when TSF is added even six hours later; however, no proliferation was observed when cells were pulsed with TSF for one hour and fresh PMA was added at different times including 24 hours later. We plan to further test the consequent hypothesis that activation may involve the induction of cell surface receptors for the TSF by PMA, PHA, or Con A.

We will pursue the biochemical characterization and purification of TSF. Using a S-200 gel filtration column, we have already begun the molecular weight determination of TSF. We are also testing the ability of TSF to bind to phenyl sepharose and hydroxylapatite columns so that we may develop a sequential purification scheme. We also plan to do isoelectric focusing. Once we have biochemically characterized TSF we can more easily determine the relationship of TSF to the IL 2 molecules described in other species.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00316-01 LMI									
PERIOD COVERED October 1, 1980 - September 30, 1981											
TITLE OF PROJECT (80 characters or less) Biochemical Characterization of Biological Mediators in the Immune Response											
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Krakauer, T.</td> <td style="width: 33%;">Staff Fellow</td> <td style="width: 33%;">LMI NIDR</td> </tr> <tr> <td>Oppenheim, J. J.</td> <td>Medical Officer</td> <td>LMI NIDR</td> </tr> <tr> <td>Carter, C.</td> <td>Microbiologist</td> <td>LMI NIDR</td> </tr> </table>			Krakauer, T.	Staff Fellow	LMI NIDR	Oppenheim, J. J.	Medical Officer	LMI NIDR	Carter, C.	Microbiologist	LMI NIDR
Krakauer, T.	Staff Fellow	LMI NIDR									
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Carter, C.	Microbiologist	LMI NIDR									
COOPERATING UNITS (if any)											
LAB/BRANCH Laboratory of Microbiology and Immunology											
SECTION Cellular Immunology Section											
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md.											
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:									
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS											
SUMMARY OF WORK (200 words or less - underline keywords) <u>Human monocytes</u> are activated by endotoxin and other inflammatory microbial products to produce hormone-like factors such as <u>Interleukin 1 (IL 1)</u> . IL 1 enhances lymphocytes mitogenic responses to lectins and thus appears to be a nonspecific lymphocyte activating signal that acts jointly with the antigen or polyclonal stimulant to stimulate T cell activation. Partial purification of IL 1 has been accomplished by the use of ultragel AcA 54 column chromatography and affinity chromatography on octyl agarose. Screening of human macrophage cell lines for the production of IL 1 is underway to enable us to produce large quantities of IL 1 for biochemical purification and molecular cloning of the IL 1 gene.											

OBJECTIVES:

1. To purify and chemically define the structures and specificity of several of the regulatory molecules produced by human monocytes and lymphocytes in immunological responses and to study the mechanisms by which they act on target cells.

2. To use recombinant DNA technology to clone the genes for these mediators. The cloned cDNA can be used to study the regulation of the production of these factors.

METHODS:

Monocytes are obtained from buffy coat fractions of peripheral blood (provided by NIH Blood Bank) after Ficoll-Hypaque gradient separation and adherence to tissue culture flasks. These adherent cells are stimulated to produce IL 1 by *E. coli* lipopolysaccharide. IL 1 is bioassayed for its mitogenic effect for lectin-stimulated murine (C3H/HeJ) thymocytes.

MAJOR FINDINGS:

1. Chromatography of crude IL 1 from human monocytes on ultrogel AcA 54 separates IL 1 from HSA. IL 1 also binds to octyl agarose and can be eluted from the gel matrix with ethylene glycol. Unlike the murine IL 1, human IL 1 does not bind to phenyl sepharose which permits its separation from the bulk of serum proteins.

2. We have obtained and are maintaining a number of macrophage cell lines and promyelocytic leukemia cell lines. Preliminary studies indicate that the "Togawa" line produces some IL 1 activity upon stimulation with LPS. Experiments are underway to optimize the production of IL 1 by synchronizing the cells before stimulation or by the use of dimethylsulfoxide to cause differentiation of these promyelocytic cell lines so that they might respond to the stimulants commonly used to activate macrophages.

3. An improved assay for IL 1 is being developed. This assay is an adaptation of the CT6 cell line (an IL 2 dependent T cell line) assay for IL 2. IL 1 in conjunction with a mitogen (Con A or PMA) stimulates a T cell line (HSB 2) to produce IL 2 which in turn can be assayed by proliferative response of CT6 cells. An improved assay with higher sensitivity is essential to the cloning of the gene.

BIOMEDICAL SIGNIFICANCE:

Lymphokines and monokines are potent mediators that can regulate immunological and inflammatory responses. Molecular cloning and purification of these mediators may permit therapeutic applications of these molecules or their antibodies to control specific steps in host defense and inflammation.

PROPOSED COURSE:

We will continue to look for cell sources which can produce large amounts of these monocyte and lymphocyte mediators in an attempt to obtain enough material to purify and biochemically characterize these regulatory

molecules. The interaction of these mediators with target cell receptors and the mechanism of how such molecules modulate proliferation and differentiation can be studied with more chemically defined material. We are also going to clone the gene for IL 1 by cloning cDNA sequences. Partially purified factors will also be used to make higher affinity monoclonal antibodies which can be used to screen for translation products of mRNA. We can then utilize cDNA clones and genomic clones to produce large amounts of gene products and for selected gene transfer to study the regulation of the expression of such proteins.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00317-01 LMI
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Macrophage Hydrogen Peroxide Inducing Factor: Biochemical Purification and Determination of its Role in Immune and Inflammatory Responses		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Gately, C. Weedon, L. Oppenheim, J. J. Pick, E. Mizel, D.	Staff Fellow Biologist Medical Director Visiting Scientist Chemist	LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any) Tom Fleischer, WRAIR, Washington, D. C.		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Cellular Immunology Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md. 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
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SUMMARY OF WORK (200 words or less - underline keywords) The ability of <u>macrophages</u> to release <u>hydrogen peroxide</u> (H_2O_2) has been correlated with their ability to kill <u>bacteria</u> and tumor cells. With this observation in mind, a rapid, quantitative microassay for the measurement of H_2O_2 has been developed and several <u>human monocyte</u> cell lines that can be induced to produce H_2O_2 have been identified. The H_2O_2 accumulation is assayed by the horseradish peroxidase-mediated <u>increase in absorbance of phenol red</u> . Utilizing this technology a lymphokine has been found to be produced by some <u>human T cell</u> <u>lines</u> that stimulates increased H_2O_2 production in <u>target human monocyte</u> <u>cell lines</u> . Biochemical studies to purify and characterize this factor have been initiated.		

MAJOR FINDINGS:

Studies to date have focused first on the development of a rapid, reliable, quantitative assay for H_2O_2 in order to facilitate purification of the lymphokine which induces H_2O_2 production in target monocytes. It has been found that cells from the human monocyte cell lines HL60 and U937 produce increased levels of H_2O_2 after incubation for 48 hr. in the presence of a lymphokine containing lymphocyte cell line supernatants. After the incubation period the culture medium with or without lymphokine is replaced by a balanced salt solution containing phenol red, horseradish peroxidase (HRPO), and phorbol myristate acetate (PMA). H_2O_2 accumulation is measured by the increase in absorbance of phenol red mediated by HRPO. The assay employs an automatic 8-channel photometer which measures absorbances vertically through the individual wells of a microtiter plate. Thus the absorbances can be determined directly from the microtiter plate, with the cells in situ.

It has also been determined that the human T cell line, HSB2, can be stimulated to produce lymphokines by a combination of Concanavalin A and PMA. Such a cell line can be rapidly expanded to produce large amounts of the H_2O_2 inducing factor, thus facilitating purification efforts.

Preliminary biochemical characterization indicates that this lymphokine activity is resistant to heating at $56^\circ C$ for 1 hr and is also non-dialyzable. It has also been determined that the molecule has some hydrophobic character since it binds to and can be eluted from phenyl sepharose. In addition, the dose-response curve of the activity is linear, indicating that probably only 1 factor is responsible for the biological activity.

SIGNIFICANCE TO BIOMEDICAL RESEARCH

As an in vitro correlate of cell-mediated immunity, the factor(s) responsible for the activation of macrophages to produce H_2O_2 may play a central role in the inflammatory process. Many factors influencing macrophages have been described on the basis of their biological activities in vitro. Progress in the detailed characterization of individual lymphokines, however, has proceeded slowly. In some cases it is unclear whether various biologic activities are attributable to distinct substances or whether some may represent different manifestations of a single substance. Also unknown are the mechanisms of action of various lymphokines and the roles which they may play in naturally occurring phenomena in vivo. To answer these questions it is necessary to study a lymphokine in a rigorous manner, subjecting it to precise physicochemical characterization and isolating the substance in a purified state. The understanding of the molecular mechanisms involved in the inflammatory process should provide a basis by which the cycle of events from antigen stimulation to inflammation may be manipulated to benefit the host.

PROPOSED COURSE

During the coming year work will focus primarily on the purification and characterization of the H_2O_2 inducing factor and its relationship to other lymphokines that activate macrophages. This will be accomplished by a variety of fractionation procedures including salt fractionation, ion exchange chromatography, gel filtration, hydrophobic chromatography, isoelectric focusing, and polyacrylamide gel electrophoresis. Whether a given technique can be used successfully for purification of H_2O_2 inducing activity will have to be determined empirically. Upon successful completion of lymphokine purification, antibody to the factor will be prepared by techniques yielding monoclonal antibodies. Such an antibody will be used to determine the role of the H_2O_2 -inducing factor in immune phenomena in vitro.

In addition studies will be pursued in collaboration with Dr. Tom Fleisher to determine whether patients with Hodgkin's disease produce a higher level of H_2O_2 inducing lymphokine than do normal donors, and whether these patients' monocytes are hyperactive with regard to H_2O_2 production when compared to normal donors.

REFERENCES

1. Pick, E. and Mizel, D. 1981. Rapid microassays for the measurement of superoxide and hydrogen peroxide by macrophages in culture using an automatic enzyme immunoassay reader. J. Immunol. Methods, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00318-01 LMI																																
PERIOD COVERED October 1, 1980 through September 30, 1981																																		
TITLE OF PROJECT (80 characters or less) The functions of phagocytes in human gingival exudate.																																		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Charon, Jacques</td> <td style="width: 33%;">Visiting Fellow</td> <td style="width: 15%;">LMI</td> <td style="width: 19%;">NIDR</td> </tr> <tr> <td>Hoffeld, Terry</td> <td>Dental Officer</td> <td>LMI</td> <td>NIDR</td> </tr> <tr> <td>Donahue, Agnes</td> <td>Dental Officer</td> <td>CIPCB</td> <td>NIDR</td> </tr> <tr> <td>Fox, Philip</td> <td>Dental Officer</td> <td>LMI</td> <td>NIDR</td> </tr> <tr> <td>Gallin, John</td> <td>Medical Officer</td> <td>LCI</td> <td>NIDR</td> </tr> <tr> <td>Pick, Edgar</td> <td>Visiting Scientist</td> <td>LMI</td> <td>NIDR</td> </tr> <tr> <td>Mergenhausen, Stephan</td> <td>Research Microbiologist</td> <td>LMI</td> <td>NIDR</td> </tr> <tr> <td>Mizel, Diane</td> <td>Chemist</td> <td>LMI</td> <td>NIDR</td> </tr> </table>			Charon, Jacques	Visiting Fellow	LMI	NIDR	Hoffeld, Terry	Dental Officer	LMI	NIDR	Donahue, Agnes	Dental Officer	CIPCB	NIDR	Fox, Philip	Dental Officer	LMI	NIDR	Gallin, John	Medical Officer	LCI	NIDR	Pick, Edgar	Visiting Scientist	LMI	NIDR	Mergenhausen, Stephan	Research Microbiologist	LMI	NIDR	Mizel, Diane	Chemist	LMI	NIDR
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SUMMARY OF WORK (200 words or less - underline keywords) <p> We have defined and compared some of the functions <u>in vitro</u> of <u>poly-morphonuclear neutrophils</u> collected from either <u>peripheral blood</u> (PB-PMN) or <u>gingival exudate</u> (CR-PMN) in healthy human subjects. We have shown that CR-PMN have a diminished capacity to further <u>phagocytose</u> opsonized particles <u>in vitro</u> as compared to PB-PMN and that a smaller proportion of CR-PMN bear <u>Fc receptors</u> for IgG than PB-PMN. We have demonstrated that there are more activated PMN in the gingival exudate than in the blood but that those activated CR-PMN apparently produce less <u>superoxide</u> anion per cell than the PB-PMN. We have also observed that CR-PMN have a diminished capacity to <u>migrate in vitro</u>. These different functions have been studied to define baseline data for further studies of the same functions of PMN from patients with diseased periodontium. In addition, we have developed a novel, sensitive quantitative assay for oxygen intermediates. </p>																																		

MAJOR FINDINGS:

The functions of polymorphonuclear neutrophils in host defense are the phagocytosis and killing of bacteria. Oxidative events are suggested as a major mechanism of intracellular killing. In order to determine whether this host defense capacity is functional in the gingival sulcus both the phagocytic capacity of the CR-PMN and their ability to produce superoxide (O_2^-) were studied and compared to those of PB-PMN from the same healthy individuals. Crevicular exudate cells were recovered from healthy interdental areas of volunteers using the crevicular washing technique. The crevicular exudate cells consisted mainly of polymorphonuclear neutrophils with few mononuclear leukocytes; most of the CR-PMN were viable as determined by trypan blue exclusion. PB-PMN were separated from heparinized blood yielding a cell population with a similar proportion of viable PMN.

The phagocytic capacity of CR-PMN and PB-PMN was studied using an opsonized red blood cell phagocytosis assay. The results indicate that a smaller proportion of CR-PMN than PB-PMN phagocytized opsonized RBC in vitro. However a large proportion of CR-PMN was found to be associated with gingival bacteria probably ingested in vivo. It was shown also that a smaller proportion of CR-PMN than PB-PMN bind IgG coated RBCs.

The oxidative burst of CR-PMN and PB-PMN was also assessed using a nitroblue tetrazolium (NBT) reduction assay. Non-stimulated CR-PMN and PB-PMN presented significantly more NBT positive cells than non-stimulated PB-PMN. Nearly 100% of both CR-PMN and PB-PMN were NBT positive when stimulated with phorbol myristate acetate (PMA). The percentage of NBT positive CR-PMN was significantly decreased by lipopolysaccharide (LPS) stimulation while that of PB-PMN was significantly increased when using the same stimulus.

The production of O_2^- by CR-PMN and PB-PMN was quantitatively measured using a new cytochrome-c reduction microassay. When stimulated with PMA both CR-PMN produced equivalent amounts of superoxide. Incubation of either CR-PMN or PB-PMN with LPS failed to increase the O_2^- production above the non-stimulated values. No significant differences were found between the production of superoxide by CR-PMN and PB-PMN in this assay.

Our data demonstrate that gingival exudate PMN are viable and capable of performing 2 major functions: phagocytosis and the oxidative burst. In addition, the difference in the NBT assay between the non-stimulated CR-PMN and PB-PMN represents a difference in the percentage of activated cells, although the total amount of O_2^- produced by CR-PMN is not greater than PB-PMN.

A novel test for the measurement of nitroblue tetrazolium (NBT) reduction by phagocytic cells was developed. Macrophages were cultured as monolayers in 96 well flat bottom tissue culture plates. They were covered with a solution of NBT and stimulated by agents known to induce an oxidative burst. The amount of reduced NBT present in the macrophages was determined by using an automatic enzyme immunoassay reader fitted with a 550 nm filter which measures and records absorbances vertically through individual wells. We found that massive NBT reduction by macrophages was induced by PMA, formyl-methionyl-leucyl-phenylalanine (FMLP) or

the Ca^{++} ionophore A23187. Less active inducers were Con A and phospholipase C. When NBT reduction was compared to extracellular O_2^- production as measured by cytochrome c reduction, it was found that there was only partial correlation. Thus, while PMA was active in both assays, FMLP and A23187 were much more active stimulants of NBT reduction than of O_2^- production. This discrepancy, which has not been reported before, might be due to the reduction of NBT by a non- O_2^- product or the production of O_2^- at intracellular sites which are only accessible to the NBT, taken up by the cells; O_2^- produced within the cells might never leave the cell as such and would therefore be incapable of reducing extracellular cytochrome c.

PUBLICATION:

1. Pick, E. and Mizel, D. Rapid microassays for the measurement of superoxide and hydrogen peroxide production by macrophages in culture using an automatic enzyme immunoassay reader. J. Immunol. Methods, in press.

OBJECTIVES:

To test the hypothesis that polymorphonuclear neutrophils are essential to protect the host periodontal tissues against deleterious effects of bacteria by the following approaches:

1. Comparing the clinical status of the periodontium of patients with specific PB-PMN defects to that of matched healthy individuals.
2. Studying the specific neutrophil functions of PMN collected from peripheral blood and gingival exudate of both patients and controls.

METHODS EMPLOYED:

1. Collection of gingival leukocytes by the crevicular washing technique.
2. Collection of peripheral blood by venepuncture.
3. Determination of the clinical periodontal status using Gingival Index, Plaque Index and loss of attachment.
4. In vitro determination of phagocytosis function of PMN using opsonized particles.
5. In vitro determination of availability of IgG and C3b receptor using a rosette assay.
6. In vitro determination of the capacity of PMN to reduce nitro-blue tetrazolium.
7. In vitro determination of the capacity of PMN to produce superoxide using a cytochrome-c reduction assay.
8. In vitro determination of the chemotactic function of PMN using a modified Boyden chamber.

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

1. Define the role of PMN in the protection of gingival tissues against dental plaque microorganisms.
2. Contribute to a better understanding of the pathogenesis of the periodontal diseases.
3. Possibly develop new diagnostic tools to assay the state of activity of periodontal diseases.
4. Provide new approaches for periodontal therapy of patients suffering from periodontal disease associated with severe defects of peripheral blood PMN.

PROPOSED COURSE:

We propose to continue these studies in several different ways:

1. To follow longitudinally the periodontal status and CR-PMN functions in patients with severe PB-PMN defects.
2. To further determine the underlying reasons for the apparent defect of further phagocytosis by CR-PMN which contain phagocytosed bacteria.
3. To define factor(s) present in the gingival sulcus which control or regulate the oxidative metabolism of CR-PMN.
4. To contribute and improve definition of functions and importance of exudate PMN in general.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00046-10 LMI
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Role of Inflammatory Lymphocyte and Macrophage Mediators in Connective Tissue Metabolism		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Wahl, S. M. Wahl, L. M. Matsuda, K. Helsel, W. McCarthy, J. B.	Research Microbiologist Research Biologist Visiting Fellow Microbiologist Microbiologist	LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any) Ronald Wilder, NIAMDD, NIH		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Humoral Immunity Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md.		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Certain connective tissue diseases appear to be the consequence of <u>cell mediated immune reactions</u> . Our current investigations focus on the mechanisms by which lymphoid cells may regulate <u>connective tissue metabolism</u> in normal and pathological conditions associated with <u>inflammatory reactions</u> . Depletion of lymphoid cells in <u>rheumatoid arthritis</u> patients by continuous flow-cell separation (lymphophoresis) results in clinical improvement in certain patients. Furthermore, in an experimental rat model, the appearance of arthritis appears to require recovery of lymphoid cell function following streptococcal cell wall induced immunosuppression, further defining a role for lymphoid cells in the etiology of this disease. <u>In vitro</u> , <u>lymphocyte mediators stimulate fibroblast proliferation</u> and collagen synthesis and also activate <u>macrophages</u> . Activation of macrophages influences connective tissue destruction through the production of <u>collagenase</u> and <u>prostaglandins</u> and can also modulate connective tissue formation through the production of monokines which stimulate fibroblast migration (<u>chemotaxis</u>), proliferation and collagen synthesis. These lymphocyte and macrophage products may provide the molecular link between the inflammatory response and the subsequent changes in connective tissue which <u>accompany inflammation</u> .		

OBJECTIVES:

Research in this laboratory focuses on characterization of the mechanisms by which the immune system may modulate connective tissue metabolism. Connective tissue metabolism is markedly altered in many inflammatory lesions. The co-existence of inflammatory cells and connective tissue cells in such lesions led us to investigate whether lymphocytes and macrophages could influence degradation of collagen and the connective tissue matrix and whether these same cells could direct the repair of this tissue injury following the inflammatory response. The repair of tissue injury, which may be extensive in chronic inflammation, can result in irreversible replacement of the original tissue by collagen. This collagen production and fibrosis then not only serve to repair the damaged tissue, but may also cause fibrotic organ damage leading to organ dysfunction. Because of the participation of fibroblasts in the final outcome of many inflammatory lesions, it is important to understand what regulates their activities under these circumstances. We have investigated how macrophages and lymphocytes modulate the fibrotic response by the release of inhibitory or facilitatory soluble signals in vitro.

In addition, since arthritis involves both hyperplasia of connective tissue components as well as destruction of the connective tissue matrix, this disease is suited to studying the possible mechanisms whereby inflammatory cells might regulate both of these pathophysiologic changes in connective tissue. An experimental rat model of streptococcal cell wall induced arthritis and human subjects with rheumatoid arthritis have been utilized to assess the role of inflammatory cells in mediating proliferation of the synovial membrane, pannus formation and eventual joint damage and destruction.

METHODS EMPLOYED:

Methods utilized to investigate the aforementioned objectives include already published procedures for macrophage chemotaxis, lymphocyte culture and proliferation, lymphokine production, prostaglandin assay, macrophage culture and monokine production, fibronectin purification, fibroblast culture, fibroblast chemotaxis, analysis of collagen formation, isolation and culture of hepatic Kupffer cells, antibody production, and column chromatography.

MAJOR FINDINGS:

Activation of macrophages results in the production of numerous molecules including enzymes and biologically active mediators termed monokines. Guinea pig peritoneal macrophages stimulated with lipopolysaccharide or muramyl dipeptide produced a soluble factor (monokine) which activated fibroblasts to proliferate. This factor is nondialyzable, heat stable at 56°C and labile at 100°C and has a molecular weight of 40-50,000 daltons. Additionally, activated macrophages produce a molecule which is chemotactic for fibroblasts. This larger molecular weight protein does not increase random migration but is responsible for directed migration of the fibroblasts. The production of this chemotactic factor appears to be prostaglandin regulated since indomethacin inhibits its

appearance in macrophage cultures. The macrophage derived chemotactic factor is distinct from the fibroblast proliferative factor and has been characterized as the glycoprotein, fibronectin. The chemotactic activity in the macrophage supernatants could be removed by a fibronectin-specific affinity column and was inhibited in the presence of antibodies to fibronectin. Furthermore, chemotactic activity in the depleted macrophage supernatants could be restored by the addition of exogenous fibronectin. The production of fibronectin by activated macrophages may thus serve as an inflammatory mediator which in addition to its other functions can recruit fibroblasts to an area of damaged tissue where they can proliferate and form the scar tissue necessary for tissue repair.

A single injection of group A streptococcal cell wall fragments induces inflammatory polyarthritis in rats. The active lesions are associated with the localization and persistence of cell walls in macrophages. The persistence of chronic inflammation in the joints is genetically determined since some strains are responders while others are not. A responder (Lewis) and a non responder (Fisher) strain of rats were selected and injected with streptococcal cell walls. Immunological functions (lymphocyte proliferation, lymphokine production and macrophage prostaglandin and monokine synthesis) were assessed in these two strains at intervals from 18 hr to 4 months after cell wall injection to determine whether the genetically dependent expression of the disease was mediated through the immune system. While both Lewis and Fisher rats were severely immunosuppressed following treatment, the Lewis (responder) strain recovered immune functions earlier than the Fisher, suggesting that normal lymphocyte function is essential in the development of the arthritic inflammation. The immunosuppression appears to be a function of macrophages and the nature of the suppressor mechanism is currently being defined. Suppression is not dependent upon H_2O_2 or O_2 generation, $IL\ 2$ depletion, excess arginase or prostaglandins. However, removal of macrophages does ameliorate the suppressive response.

In related studies, immune function is being investigated in rheumatoid arthritis patients and in normal individuals. Twenty-four rheumatoid arthritis patients were screened for monocyte chemotactic responses and for lymphoproliferative responses in parallel with healthy subjects. The arthritis patients displayed a defect in monocyte migration towards C5a, FMLP and lymphocyte derived chemotactic factor as compared to normals. Rheumatoid arthritis patients generally fall into three categories with respect to lymphoproliferative responses: suppressed lymphocyte proliferation to antigens and mitogens, normal response, or those with limited suppression. Since lymphocytes play a significant role in perpetuating the inflammatory synovitis of rheumatoid arthritis, lymphocyte depletion has been used to ameliorate synovitis. However, some patients do not benefit from this procedure (lymphophoresis) and it appears that one can determine to some extent which patients will benefit and which will not benefit from lymphophoresis based upon their immunologic status prior to treatment. Markedly immunosuppressed patients respond better than those with limited suppression and those without detectable suppression do not benefit from the lymphophoresis treatment. Lymphophoresed cells are separated by elutriation into B lymphocytes, T lymphocytes and monocytes and these cells are analyzed during the course of lymphophoresis for changes in function. In the suppressed patients, one sees an enhancement of lymphocyte and monocyte activity as lymphophoresis proceeds, suggesting a depletion of suppressor cells.

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

Cellular immune phenomena are the basis for the development of many chronic inflammatory lesions. There are certain pathologic conditions including scleroderma, pulmonary fibrosis, and schistosomiasis which have been characterized as cell-mediated which lead to excessive connective tissue formation or fibrosis. It is possible that the changes in the connective tissue could be mediated by the local production and release of lymphokines by antigen-activated lymphocytes. Lymphokines appear to regulate fibroblast function suggesting a pathway for enhanced connective tissue metabolism including collagen formation. Additionally, macrophages which are a predominant cell in these inflammatory loci can generate chemotactic signals responsible for the mobilization and recruitment of fibroblasts. Release of additional monokines stimulates fibroplasia and connective tissue deposition. Ultimately, collagen production and fibrosis terminates the inflammation. Whereas fibrosis is a normal repair process following tissue injury, in chronic inflammation, such as that found in granulomatous diseases, the irreversible fibrosis may lead to organ damage with a potentially fatal outcome. Activated lymphocytes may also be largely responsible for the production of chemotactic stimuli which attract macrophages to sites of infection or inflammation. Once localized at such a site, these macrophages may be activated to produce a number of enzymes and to release soluble factors (prostaglandins, fibroblast activating factor, etc.), which influence other cells. If continuously activated as in chronic inflammatory lesions like periodontal disease and rheumatoid arthritis, these cells may contribute to the pathologic tissue destruction by the release of lysosomal enzymes, collagenase, and prostaglandins. Thus, through an understanding of the way these cells are triggered, it may be possible to control or modulate their functions, thereby altering the course of the disease.

PROPOSED COURSE:

Investigations are continuing into the mechanisms of induction of fibrosis associated with inflammation which in some cases may progress to chronic pathologic lesions. Areas of study will focus on the interaction between the lymphoid system and connective tissue components. Lymphocytes and macrophages appear to be able to influence fibroblast growth and thereby may provide a pathway for normal connective tissue repair following injury and/or for the markedly altered connective tissue changes which occur in various pathologic conditions. These studies will be pursued both in our in vitro model and also in the in vivo model of hepatic granulomas associated with streptococcal cell wall injections. Characterization of the soluble mediators produced by the lymphocytes and macrophages will be correlated with the mediators released from active granulomas. The role of fibronectin produced by macrophages will also be explored both in the regulation of fibroblast function and in its mechanism of production by macrophages. The production of monoclonal antibodies to fibronectin will facilitate these investigations. That the same types of inflammatory cells are involved in lesions characterized by destruction as are in those characterized by excessive connective tissue formation is clear, but it is not known what mechanisms tip the balance in favor of one or the other. According to this dual role, inflammatory cells may contribute to tissue destruction and yet may also be critical in the initiation of fibroplasia and the remodelling of the fibrotic tissue.

Regulatory disturbances of inflammatory cell function may create an exaggeration of one or the other role. Continuing research appears to be essential in this area to understand the immunologic pathogenesis of these and other connective tissue disorders. Isolation of synovial inflammatory cells will enable characterization of the subpopulations of cells involved in an in vivo inflammatory response. The isolation of these cells should enable analysis of the interactions of these cells with synovial connective tissue cells and elucidate some of the mechanisms involved in this chronic inflammatory lesion. Further efforts will also be directed at establishing criteria for lymphoproliferating rheumatoid arthritis patients. Analysis of subpopulations of lymphocytes which may be malfunctioning in this disease through the use of functional assays and by identifying the cells with monoclonal antibodies directed at cell surface markers will be useful in understanding the pathogenesis of the disease.

PUBLICATIONS:

1. Wahl, S. M. 1981. Inflammation and wound healing. In The Cell Biology of Immunity and Inflammation. (J. J. Oppenheim, D. Rosenstreich and M. Potter eds.). Elsevier North Holland Biomedical Press, New York, in press.
2. Wahl, L. M., J. B. McCarthy, C. E. Olsen, S. M. Wahl, A. L. Sandberg and S. E. Mergenhagen. 1981. Regulation of macrophage collagenase by prostaglandins and cAMP. In Endogenous Mediators in Host Responses to Bacterial Endotoxin.
3. Wahl, S. M. and L. M. Wahl. 1981. Modulation of fibroblast growth and function by monokines and lymphokines. Lymphokine Reports: 2: 179.
4. Wahl, S. M. 1981. The role of mononuclear cells in the wound repair process. In The Biology and Management of Surgical Wounds (Shires, J. T. ed.) Lea & Febiger, Philadelphia. In press.
5. Wahl, L. M. and S. M. Wahl. 1981. Regulation of connective tissue metabolism by the immune system. In Immunology of the Eye. Immunological Aspects of Ocular Disease. Infection, Inflammation and Allergy (Suran, A. A., Gery, I. and Nussenblatt, R., eds.) 3: 291-302.
6. Wahl, S., Y. Tsukamoto, R. Obrist, J. B. McCarthy and S. E. Mergenhagen. 1981. Stimulation of fibroblast activity by soluble mediators from inflammatory and neoplastic cells. In Connective Tissue of the Normal and Fibrotic Human Liver. (Gerlach, U., G. Pott, J. Rauterberg and B. Vob, eds.). F. Thieme Verlag, Stuttgart-New York. In press.
7. Tsukamoto, Y., W. E. Helsel and S. M. Wahl. 1981. Macrophage production of fibronectin, a chemoattractant for fibroblasts. J. Immunol. 127: 673.
8. Wahl, S. M. 1981. Mononuclear cell mediated alterations in connective tissue host bacterial interactions in periodontal disease. (S. E. Mergenhagen and R. Genco. eds.). In press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00061-08 LMI
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Tumor Specific Antibody with Chemotactic Activity		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Sandberg, A. L. Obrist, R. Pazoles, P.	Research Biologist Visiting Associate Chemist	LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Humoral Immunity Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, MD, 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <u>Host defense against tumors</u> might be augmented by enhancing the migration of <u>macrophages</u> into a tumor site. A reagent with the potential of producing a localized <u>chemotactic response</u> was prepared by covalently coupling rabbit anti-guinea pig hepatoma <u>antibodies</u> to the synthetic chemoattractant formyl-methionyl-leucyl-phenylalanine (fMLP). The resulting complexes were <u>chemotactic</u> for guinea pig macrophages and reacted with surface antigens and the hepatoma cells. The <u>in vivo</u> effects of the <u>antibody-fMLP complexes</u> were assessed by their intraperitoneal administration to guinea pigs which were previously injected intraperitoneally or subcutaneously with hepatoma cells. The numbers of <u>macrophages</u> infiltrating the peripheral and central areas of the <u>tumors</u> were significantly greater in those guinea pigs with <u>intraperitoneal tumors</u> which received antibody-fMLP than in those injected with phosphate buffered saline, antibody or free fMLP. The mean <u>tumor weights</u> of the groups which were injected with <u>antibody-fMLP complexes</u> were lower than those of the other four groups although these differences were not statistically significant. These initial <u>in vivo</u> investigations demonstrate that <u>antibody-chemotactic factor</u> complexes can enhance the influx of <u>macrophages</u> into tumors, a response known to favor the host's <u>tumorocidal defense mechanisms</u> .		

OBJECTIVES:

The participation of inflammatory cells in host defense against tumors may be augmented if the influx of these cells into tumor area could be enhanced. This might be accomplished by coupling a chemotactic factor to a tumor specific antibody. The goals of this project are to produce tumor specific antibodies; covalently couple them to the chemotactic peptide, f-MLP; characterize the complexes; evaluate the chemotactic and antibody binding activity of the complexes; and to determine the in vivo effects of the complexes on macrophage migration into the tumor site and tumor growth.

METHODS:

Standard methods are used for the production and purification of specific antibody, characterization of the antibody-peptide complexes, and the in vitro evaluation of the complexes (indirect membrane immunofluorescence, complement dependent cytotoxicity, chemotaxis). The in vivo responses to anti-tumor antibody-fMLP complexes are evaluated by standard histochemical analyses. Standard tissue culture techniques and radioimmunoassays are employed.

MAJOR FINDINGS:

Immunoglobulin G (IgG) reactive with a guinea pig strain specific hepatoma was covalently coupled to the synthetic chemotactic peptide, fMLP by a water soluble carbodiimide reagent. Coupling of the fMLP to the antibody was verified by coelution of tritiated fMLP and IgG protein from molecular sieve columns to which a reaction mixture containing unlabeled fMLP, tritiated fMLP, IgG and carbodiimide had been applied. The IgG fMLP complexes possessed the desired biological activity of each component; the complexes were chemotactic and reacted with surface antigens present on the tumor cells but not with those on normal liver cells or other cell types. The IgG-fMLP was also chemotactic when bound to tumor cells. This activity may be attributable to the release of IgG-fMLP, free fMLP or immune complexes consisting of tumor antigens and IgG-fMLP.

Several protocols were followed to assess the possible in vivo effects of IgG-fMLP on tumors. The groups of animals received hepatoma cells either subcutaneously or intraperitoneally. IgG-fMLP, phosphate buffered saline, IgG or free fMLP were administered intraperitoneally to subgroups of guinea pigs according to seven schedules varying from a single injection to five injections. All major organs and tumors were excised, weighed and fixed. Sections of the tumors were stained for esterase activity (an histochemical stain which is specific for macrophages) and the macrophages in the central and peripheral areas of the tumor quantitated microscopically. The feasibility of employing complexes containing tumor reactive antibodies and a chemotactic factor as therapeutic agents in some malignancies is supported by the findings that the numbers of macrophages in the intraperitoneal tumors were significantly greater in the groups of guinea pigs which received IgG-fMLP than in those which received buffer, IgG or free fMLP. Similar results were obtained in one of three experiments in which the tumors were grown subcutaneously. The

mean weights of the intraperitoneal tumors from IgG-fMLP treated guinea pigs were lower than those of the other groups but no statistically significant differences could be demonstrated because of the marked variability within each group. Differential cell counts of the peritoneal exudates revealed depressed numbers of macrophages in all the guinea pigs bearing intraperitoneal tumors regardless of the treatment regimen. In contrast, the polymorphonuclear leukocytes were elevated in the tumor bearing animals. No marked differences in other cell types were observed between non-tumor bearing and tumor bearing guinea pigs or between those groups of tumor bearing animals which received buffer, IgG, IgG-fMLP or free fMLP.

The functional capacity of the peritoneal macrophages at the time of sacrifice of the animals was assessed by examining the basal and endotoxin stimulated production of prostaglandin E_2 . Irrespective of the treatment regimen, prostaglandin E_2 production was suppressed in all the tumor bearing animals.

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

Inflammatory cells, especially macrophages, have been implicated as major effectors in in vivo tumor killing. The present studies indicate that the administration of a tumor-reactive antibody coupled to a chemotactic factor can direct the migration of macrophages to a tumor site. The significant elevation in macrophage numbers in the tumors of animals which received IgG-fMLP as well as the decreased tumor weights in these guinea pigs demonstrate that the administration of these complexes can enhance the infiltration of tumors by macrophages, a process which is known to be beneficial in the destruction of tumors.

PROPOSED COURSE:

Studies are continuing to further evaluate the in vivo effects of IgG-fMLP complexes in tumor bearing animals. Both the time of administration and the doses of IgG-fMLP, IgG, and free fMLP will be varied. Modification of tumor specific antibody with other biologically active agents (e.g. muramyl dipeptide) is also in a preliminary testing stage.

PUBLICATIONS:

1. Obrist, R. and Sandberg, A. L. In vitro effects of anti-tumor antibody-chemotactic factor complexes. Int. J. Cancer (submitted).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE-00216-05 LMI
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Immunological Control of Connective Tissue Metabolism		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Wahl, L. M. Sandberg, A. L. Wahl, S. M. Winter, C. Hochman, N.	Research Biologist Research Biologist Research Microbiologist Microbiologist Guest Worker	LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any) Ronald Wilder, NIAID, NIH Lawrence, Raisz, Univ. of Connecticut		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Humoral Immunity Section		
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md. 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The purpose of this project is to study the role of the immune system in connective tissue metabolism. Experiments with the osteopetrotic (op) rat have revealed that lymphocytes from these animals are suppressed in their proliferative responses and the macrophages are defective in chemotaxis. However, the lymphocyte from the op rat produces normal levels of chemotactic factor, the monocytes produce normal levels of lymphocyte activating factor and PGE ₂ . The possible role of macrophages in streptococcal cell wall (STC CW) induced adjuvant arthritis in rats was examined by obtaining peritoneal macrophages from Lewis (susceptible) or Fisher (resistant) rats at various times after injection of STCCW. Macrophages from STCCW injected Fisher rats produced more PGE ₂ than the non-injected controls while there was no difference in macrophage PGE ₂ production between control and injected Lewis rats. However macrophages from Lewis rats produced significantly less PGE ₂ than macrophages from Fisher rats. In studies dealing with peripheral blood cells from normal volunteers and rheumatoid arthritis patients we have modified the technique of counterflow centrifuge elutriation to separate large numbers of B cells, T cells and monocytes into relatively pure populations.		

OBJECTIVES:

Our goal in this project is to examine the role of macrophages and lymphocytes in connective tissue destruction.

MAJOR FINDINGS:

We have previously initiated a series of studies dealing with the role of the immune system in bone resorption by utilizing osteopetrotic mice and rats. Recent experiments in this area have focused on the osteopetrotic (op) rat. Examination of the proliferative response of spleen cells and thymocytes to mitogens revealed that the lymphocytes from op rats were hypoproliferative when compared to lymphocytes from normal littermates. Since the op lymphocytes were defective in their ability to proliferate they were tested for other possible differences in function. When supernatants from op and normal lymphocytes were tested for their chemotactic activity on macrophages and fibroblasts there were no differences. Thus, although the proliferative capacity of the op lymphocytes is impaired, their ability to produce chemotactic factor is not. Macrophages from op rats were defective in their chemotactic response to C5a and lymphokines. Op macrophages were also defective in the production of chemotactic factor for fibroblasts. However when activated and tested for the production of PGE₂ or lymphocyte activating factor there was no difference between macrophages from op and nonaffected littermates. These results indicate that only certain biological functions of the lymphocytes and the macrophages from op rats are defective and may contribute to the lack of bone resorption in this animal model.

We are in the process of examining human lymphocytes and monocytes obtained by lymphophoresis of normal volunteers and rheumatoid arthritis (RA) patients. We have obtained large numbers of pure B cells, T cells and monocytes by modifying the technique of counterflow centrifugal elutriation. This technique involves pumping Ficoll-Hypaque separated peripheral blood cells into a chamber(s) in a centrifuge head which is maintained at a constant speed. The cells are loaded into the chamber at a flow rate which will allow them to collect in the chamber without exiting. A total of 2×10^9 cells can be purified when two loading chambers are used in the centrifuge head. Following loading of the cells, the flow rate is gradually increased causing the cells to exit the chamber and centrifuge head against the centrifugal force resulting in fractionation of cells from the least dense to the most dense. Characterization of these fractions by staining and cell sorting has revealed that individual fractions can be obtained which contain 40-75% B cells, 95% T cells and 85-97% monocytes. Moreover, this procedure unlike other cell purification techniques, completely separates B cells from monocytes. The ability to separate large numbers of relatively pure B cells, T cells and monocytes has allowed us to begin characterizing possible functional differences in cells obtained from rheumatoid arthritis patients and normal volunteers in an attempt to further understand the function of immunologically competent cells in this disease.

In collaboration with Dr. Ronald Wilder (NIAMD), we have initiated a study to evaluate the immune system of rats in which adjuvant arthritis has been induced by streptococcal cell walls (STCCW). We have utilized

the Lewis rat which is susceptible to induction of adjuvant arthritis by STCCW and the Fisher rat which is resistant. STCCW were injected into these animals and 6 and 16 weeks later oil induced peritoneal macrophages were harvested, cultured and the media from control and STCCW or endotoxin stimulated cultures evaluated for PGE_2 levels. Macrophages from Fisher injected (STCCW) rats released high levels of PGE_2 into the media compared to macrophages from control Fisher rats (noninjected). When macrophages from the injected Fisher rats were stimulated in vitro they did not produce increased levels of PGE_2 whereas the macrophages from noninjected rats did. Macrophages from the Lewis injected or noninjected rats produced equal amounts of PGE_2 , which were significantly less than those produced by macrophages from Fisher injected rats. Moreover PGE_2 produced by macrophages from the Lewis control and injected rats could be enhanced with STCCW whereas the Fisher rat macrophages, which were activated in vivo by STCCW, were refractory to further activation in vitro. These results suggest that the in vivo activation of the Fisher rat macrophages by STCCW results in the rapid clearance of STCCW while macrophages from Lewis rats which are not activated in vivo, may allow the accumulation of STCCW in the joints of these animals leading to a local inflammatory response. This may explain why Fisher rats are resistant to the induction of adjuvant arthritis while Lewis rats are susceptible.

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

Chronic inflammatory lesions such as periodontal disease and rheumatoid arthritis are associated with immunological alterations which lead to loss of bone and cartilage. Our present studies have focussed on furthering the understanding of the changes in immunological response which brings about these destructive conditions. The results from the osteopetrotic rat indicate that defects in both lymphocyte and macrophage functions may be associated with the loss of bone resorption capability. In the adjuvant arthritis rat model it appears that the ability of the macrophage to be activated at the site of inflammation may be a determinant in the pathology of arthritis. The ability to separate large numbers of B cells, T cells and monocytes by counterflow centrifugal elutriation will permit function studies on the interaction of these cells and comparison of these populations between normal individuals and rheumatoid arthritis patients.

PROPOSED COURSE OF STUDY:

The projects involving the osteopetrotic model, adjuvant arthritis and rheumatoid patients will continue in an attempt to further define the role of lymphocytes and monocytes in chronic inflammatory lesions. Since suppression of the immune system appears to be involved to some degree in each of these pathological events, we will study the mechanism of suppression. It is believed that some of the products associated with the prostaglandin pathways are involved in the process of immune suppression. In order to fully examine and compare the various prostaglandin products produced by the immune system in the normal and disease state we will utilize the technique of high pressure liquid chromatography (HPLC) in the identification of the full spectrum of prostaglandins. Counterflow centrifugal elutriation of peripheral blood cells spleens and peritoneal exudates from the varying normal and disease

states described here will continue in an attempt to evaluate abnormal functions in pure cell preparations or in the interactions between pure cell populations which may account for the etiology of these pathological conditions. Work will also continue on the sequence of macrophage activation which leads to the production of collagenase. In this regard the possible role of the ornithine decarboxylase pathway in the activation sequence of macrophages will be evaluated.

PUBLICATIONS:

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 DE-00254-04 LMI									
PERIOD COVERED October 1, 1980 - September 30, 1981											
TITLE OF PROJECT (80 characters or less) Microbial Antigens Associated with Specific Adherence											
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Cisar, J. O.</td> <td style="width: 33%;">Research Microbiologist</td> <td style="width: 33%;">LMI NIDR</td> </tr> <tr> <td>Curl, S. H.</td> <td>Microbiologist</td> <td>LMI NIDR</td> </tr> <tr> <td>Sandberg, A. L.</td> <td>Research Biologist</td> <td>LMI NIDR</td> </tr> </table>			Cisar, J. O.	Research Microbiologist	LMI NIDR	Curl, S. H.	Microbiologist	LMI NIDR	Sandberg, A. L.	Research Biologist	LMI NIDR
Cisar, J. O.	Research Microbiologist	LMI NIDR									
Curl, S. H.	Microbiologist	LMI NIDR									
Sandberg, A. L.	Research Biologist	LMI NIDR									
COOPERATING UNITS (if any) Othmar Gabriel, Georgetown University; Floyd C. McIntire, George Revis and Albert E. Vatter, University of Colorado Medical Center											
LAB/BRANCH Laboratory of Microbiology and Immunology											
SECTION Humoral Immunity Section											
INSTITUTE AND LOCATION National Institute of Dental Research, Bethesda, Md. 20205											
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:									
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>											
SUMMARY OF WORK (200 words or less - underline keywords) Studies are continuing toward defin- ing the mechanisms by which oral <u>actinomycetes</u> adhere to other <u>plaque bacteria</u> and to mammalian cells. One important mechanism involves a lactose-inhibitable, cell- associated <u>lectin</u> on human strains of <u>Actinomyces viscosus</u> and <u>A. naeslundii</u> . The results of three independent experimental approaches have associated the lectin activity on these bacteria with <u>fimbriae</u> (i.e. <u>pili</u>) of a single antigenic type, designated Ag 2. These results involve: (i) detection of the lectin activity of purified Ag 2 fimbriae; (ii) blocking of lactose-sensitive adherence by Fab frag- ments against the Ag 2 fimbriae; and (iii) the complete absence of Ag 2 fimbriae on mutant bacterial strains which are specifically defective in lactose-sensitive adherence. In addition to Ag 2 fimbriae, many actinomycete strains have been shown to possess fimbriae of an additional antigenic type, designated Ag 1. Several <u>mono-</u> <u>clonal antibodies</u> have been produced against the Ag 1 structures and have served as reagents for purifying these components and for studying their functions. The Ag 1 fimbriae lack detectable lectin activity but may contribute to certain <u>ad-</u> <u>herence</u> phenomena which are not inhibited by lactose. Thus, distinct structures on the bacterial cell-surface seem to perform specific adherence functions.											

OBJECTIVES:

The continuing goals of this project are (i) to identify, isolate and characterize microbial cell-surface antigens which promote adherence; (ii) to characterize the specificities of monoclonal and secretory antibodies which effectively block microbial adherence; and (iii) to examine the effects on mammalian cells of various microbial products. The present report focuses on the identification of different types of fimbriae on the surface of Actinomyces viscosus and the involvement of these structures in microbial adherence to oral surfaces.

METHODS:

This project utilizes a variety of biochemical, immunological, bacteriological and electron microscopic techniques which have been defined. In addition, the hybridoma technique has been used to produce a number of monoclonal antibodies against different fimbriae on A. viscosus T14V. The production of these antibodies has been accomplished in collaboration with the Clinical Immunology Section.

MAJOR FINDINGS:

A lactose-inhibitable lectin activity on human strains of A. viscosus and A. naeslundii contributes to the adherence of these bacteria to various oral surfaces. Previous studies with A. viscosus T14V have resulted in the identification of two fimbrial components, designated Ag1 and Ag2, and in the production of several monoclonal antibodies against the Ag2 structure. To prepare monoclonal antibodies against Ag 1, the hybridoma technique was performed with spleen cells from BABL/c mice immunized with the partially purified antigen. These antibodies and those directed against Ag2 have been used to prepare affinity columns for the complete purification of each component. The electron microscopic examination of each isolated structure and of bacterial cells labeled with each monoclonal antibody have shown that both the Ag1 and Ag2 components have a similar fibrillar morphology. Further experiments have shown that the lactose-inhibitable lectin activity which is associated with Ag2 fimbriae, is completely absent from preparations of purified Ag1 fimbriae. These results establish the existence of two types of cell-surface structures on A. viscosus T14V and suggest an association of the lectin activity with only one component.

The results of further investigations have provided support for and have also extended the above findings. Fab fragments prepared from mono-specific rabbit antiserum against Ag2 but not antiserum against Ag1 were found to block lactose-inhibitable adherence of A. viscosus T14V. Significantly, all monoclonal antibodies against the Ag2 fimbriae also block adherence, but to date several of their Fab fragments have failed to inhibit. This observation suggests that the monoclonal Fab fragments may not be reacting in close proximity with the lectin combining site or alternatively that Fab fragments of more than a single specificity may be required to inhibit the lectin activity of the fimbriae. Further evidence which supports the role of Ag2 fimbriae in lactose-sensitive

adherence has come from the antigenic analysis of mutants isolated from A. viscosus T14V by Dr. Paul Kolenbrander of the Microbiology Section. While the T14V parent strain carried both Ag1 and Ag2 fimbriae, mutant strains specifically defective in lactose-inhibitable adherence possessed Ag1 but were completely lacking Ag2. Therefore, the combined results of three independent experimental approaches associate the cell-surface lectin activity of A. viscosus T14V with a single type of fimbriae.

Studies with monoclonal antibodies against the Ag1 and Ag2 fimbriae have shown that the findings made with A. viscosus T14V apply broadly to many human strains of A. viscosus and A. naeslundii. Thus, most isolates of these species possess Ag2 like fimbriae and exhibit the corresponding lectin activity. By contrast, Ag1 fimbriae, while present on many strains of A. viscosus and certain isolates of A. naeslundii, are absent from other strains of the later species. The further study of these Ag1 deficient strains may well provide important insights into the function(s) of these structures.

SIGNIFICANCE TO BIOMEDICAL AND DENTAL RESEARCH:

Microbial adherence represents a critical initial event in many host-parasite relationships including those which occur in the oral cavity. The results of this project favor the idea that distinct structures on the bacterial cell-surface perform specific adherence functions. They also illustrate the use of monoclonal antibodies as reagents for studying the mechanisms of microbial adherence and for identifying the antibody specificities which effectively block adherence. A better understanding of these events at the molecular level may suggest new and useful approaches for the prevention of certain bacterial infections..

PROPOSED COURSE:

Studies will continue towards the precise identification of the lectin combining site(s) on lactose-sensitive Ag2 fimbriae of A. viscosus T14V. Various monoclonal antibodies which are presently available will be assayed for their abilities to block adherence. In addition, the ability of individual antibodies to compete with each other for binding to fimbriae will be determined. Based on the results of such competition experiments, different antibodies may be tested in combinations for their ability to block adherence.

Attempts will be made to develop an assay which measures directly the binding of soluble glycoproteins by the lectin on Ag2 fimbriae. This assay may provide an approach for the selection of hybridomas which secrete monoclonal antibodies directed against the lectin combining site.

Structural studies involving the Ag1 and Ag2 fimbriae of A. viscosus T14V and certain other related strains will continue.

Certain additional ongoing studies will continue. These include attempts to identify the function of the Ag1 fimbriae of A. viscosus T14V and further efforts to identify and isolate carbohydrates which function as lectin receptors in the coaggregation of oral actinomycetes with streptococci.

PUBLICATIONS:

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00034-13 LMI
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Mechanisms of Histamine Release		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Siraganian, R. Hook, W.A. Urata, C. Camargo, S. McGivney, A. Basciano, L.K.	Chief, Clinical Immunology Research Microbiologist Visiting Fellow Guest Worker Postdoctoral Fellow Microbiologist	LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any) NIAMDD, Arthritis & Rheumatism Branch, NIH NCI, Laboratory of Cell Biology NIH NCI, Laboratory of Theoretical Biology, NIH		
NIMH, Laboratory of Clinical Science, NIH		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Clinical Immunology Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 5.75	PROFESSIONAL: 4.00	OTHER: 1.75
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <u>Histamine release from mast cells and blood basophils</u> is being studied as one of the immunological mechanisms involved in inflammation. Among the histamine releasing agents employed are IgE antibody, and the Ca^{2+} ionophore A23187. The relationships between IgE crosslinking, basophil desensitization and histamine release were analysed by kinetic studies. Cultured rat basophilic leukemia cells are used as a model for the studies of the IgE receptor and changes in phospholipid methylation during cell activation.		

I. Project Description

A. Studies On Histamine Secretion With The Rat Basophilic Leukemic Cell Lines.

The cloned rat basophilic leukemia (RBL) cell lines have been used for biochemical studies on the mechanism of exocytosis.

A study evaluated the effect of inhibitors of transmethylation on histamine release from rat mast cells and rat basophilic leukemia cells. IgE-mediated histamine release from rat basophilic leukemia cells (RBL-2H3 cells) was inhibited by 3-deazaadenosine (DZA) in the presence of L-homocysteine thiolactone (Hcy) or the combination of adenosine, erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA) and Hcy in a dose-dependent fashion. There were no significant changes in the cellular cAMP levels by these inhibitors. Histamine release induced by anti-IgE or dextran from normal rat mast cells was also blocked by DZA, plus Hcy in a dose-dependent manner. DZA at 10^{-3} M in the presence of 10^{-4} M Hcy or the combination of 10^{-3} M adenosine, 10^{-4} M EHNA and 10^{-3} M Hcy inhibited lipid (perhaps phospholipid) methylation into RBL-2H3 cells without affecting choline incorporation. In the presence of 10^{-3} M DZA plus 10^{-4} M Hcy there was a 170-fold increase in [35 S]AdoHcy with the concomitant appearance of 3-deaza-AdoHcy when the cells were incubated with [35 S]methionine, thus, indicating that these drugs inhibited methylation reaction(s) through the intracellular accumulation of AdoHcy and 3-deaza-AdoHcy. In contrast, histamine release from rat mast cells induced by the calcium ionophore A23187, compound 48/80, polymyxin B or ATP was not inhibited by these compounds. These results suggest that IgE- or dextran-mediated histamine release involves methylation reactions whereas the other secretagogues bypass this early step.

Stimulation of IgE receptors on rat basophilic leukemia cells (RBL) causes a transient rise and fall of methylated phospholipids, Ca^{2+} influx and release of arachidonic acid previously incorporated into phosphatidylcholine and liberation of histamine. Inhibition of phospholipid methylation by methyltransferase inhibitors, 3-deazaadenosine and homocysteine thiolactone, almost completely blocks the influx of Ca^{2+} and release of arachidonic acid and histamine. Stimulation of IgE receptors by antigen releases only [14 C]-arachidonic acid but not [14 C]-linoleic acid, [14 C]-oleic acid or [14 C]-stearic acid, all of which were previously incorporated into phospholipids. [14 C]-Arachidonate was found to be incorporated mainly into phosphatidylcholine. The phosphatidylcholine rich in arachidonate appeared to be synthesized to a considerable extent by the transmethylation pathway. These findings suggest that in RBL cells, IgE receptors, phospholipid methyltransferase, Ca^{2+} ion channel and phospholipase(s) that cause release of arachidonic acid and the discharge of histamine are associated.

The importance of phospholipase activation in the IgE-mediated and ionophore-induced histamine release from the rat basophilic leukemia cell line (RBL) has been examined. The activation of phospholipase(s) as measured by [14 C]-arachidonic acid release and the release of histamine both

required Ca^{2+} and were temporally parallel. Inhibition of phospholipase(s) activity by the inhibitors mepacrine and α -parabromacetophenone also correlated with the inhibition of histamine release. [^{14}C]-Arachidonic acid released by the phospholipase(s) was mainly metabolized to prostaglandin D_2 . The inhibition of the cyclooxygenase pathway by indomethacin did not affect histamine release. 5,8,11,14-Eicostatraynoic acid inhibited both histamine and [^{14}C]-arachidonic acid release suggesting an effect not only on the cyclooxygenase and lipoxygenase pathways but also on the phospholipase(s). These results suggest that activation of phospholipase appears to be necessary for histamine release in the RBL cells.

Two cloned sublines of the rat basophilic leukemia cells were mutagenized and selected for drug resistance; the lines were then recloned and tested for their histamine content, IgE receptor number, IgE-mediated cell activation resulting in methylation, Ca^{2+} influx, arachidonic acid and histamine release. The cells were also tested for ionophore-mediated Ca^{2+} influx, arachidonic acid and histamine release. A number of variants defective at different stages in the release process were recognized. These allow the sequencing of the different stages in the release process: IgE activation is followed by methylation, Ca^{2+} influx, arachidonic acid and histamine release. However, even in this sequence there are variants which demonstrate that there are intermediate steps to the sequence, i.e. in some variants IgE receptor cross-linking is not followed by methylation although the cells have both phosphomethyltransferase enzymes. Similarly, increased phospholipid methylation is not followed by Ca^{2+} influx in one variant. Clearly, such variants might have defects in "coupling" of the two events or in the Ca^{2+} channels. In other variants arachidonic acid release is not followed by histamine release. Further characterization of these variants will provide a powerful tool to analyze the pathway involved in cell secretion.

Variants of the rat basophilic leukemia (RBL) cell line were isolated and screened for phospholipid methyltransferase I and II activities (enzymes that convert phosphatidylethanolamine to phosphatidylcholine). Two variants were found which had decreased phospholipid methyltransferase enzyme levels and were unable to cause an influx of Ca^{2+} or release histamine in an IgE-mediated reaction. However, these cells were able to release histamine through an ionophore-induced reaction, indicating that the releasing mechanism distal to the Ca^{2+} channel was intact. One cell line, 1C1.B1, had low specific activity for phospholipid methyltransferase I (PMT I). A second variant, 2H3.B6, had reduced phospholipid methyltransferase II (PMT II) activity. Although both variants were unable to incorporate [methyl- ^3H]-methionine or [^3H]-serine into phosphatidylcholine, they were able to incorporate [methyl- ^3H]-choline and 2[(N)- ^3H]-inositol. Fusion of the two cell lines and isolation on selective media resulted in the growth of eight independent hybrids. All eight had an increased number of chromosomes and normal phospholipid methyltransferase activities. Stimulation of the hybrids with IgE resulted in Ca^{2+} influx and histamine release. These results indicate that phospholipid methylation precedes and is necessary for Ca^{2+} influx, and further supports the hypothesis that methylation is a necessary early step in the IgE-mediated histamine release reaction in RBL cells.

B. Study Of Receptor For IgG (Fc_γ) and IgE (Fc_ε) On The Rat Basophilic Leukemia Cells.

We have previously found receptors for both IgE and IgG on the rat basophilic leukemia cells. The subclass specificity for the binding and histamine release activities of rat IgG has been examined with a variant of the rat basophilic leukemia (RBL) cell. All four subclasses of rat IgG as well as rabbit IgG and rat IgE bound to the Fc(γ) receptor. Cross-linked oligomers of all four subclasses of rat IgG were capable of mediating histamine release whereas cross-linked rabbit IgG was not. In addition, cells saturated with IgE were still able to bind rat IgE and to release histamine through an IgE mediated reaction. This demonstrates that rat IgG binds and functionally activates a receptor other than that activated by IgE on a variant of the RBL cells.

C. Isolation and Characterization Of Mouse Mastocytoma Cell Lines.

Four mastocytoma tumors induced in mice treated with tetramethylpentadecane and infected with Abelson murine leukemia virus were obtained from M. Potter (NIH). We have isolated a cell line from each tumor. These are stable and have been carried in culture for more than one year. The lines were determined to be of mouse origin by karyotyping and by the ability to induce tumors when injected back into the mouse strains in which the tumors originated. The cells contain histamine, have IgE receptors (6×10^5 - 6×10^6 receptors/cell) and release histamine by IgE, immune complex or ionophore A23187-induced reactions.

Mouse Origin	Cell	Chromosome No. ± SE	Histamine Content ng/10 ⁶ cells	%Histamine Release		
				IgE	A23187	Immune Complex
CXBI	MMC-1	40 ± 2	230 - 670	56	51	21
CB6F ₁	MMC-8	37 ± 1	270 - 538	27	58	9
BALB/c	MMC-14	39 ± 2	99 - 392	20	20	3
CXBG	MMC-34	46 ± 2	715 - 843	17	81	15

Histamine release is optimal at 37°C, requires Ca²⁺ but does not require phosphatidylserine. In addition, we have isolated cloned sublines from each of the four lines with varying capacities for IgE, immune complex or ionophore induced histamine release. This represents the first report of stable histamine releasing mastocytoma cell lines of mouse origin.

D. Food Antigen-induced Histamine Release From The Leukocytes of Aphthous Stomatitis Patient.

The leukocytes from sixty patients with recurrent aphthous stomatitis were tested for histamine release in response to environmental and food antigens. Eighteen patients (30% of the population studied) had a history

of respiratory allergy and this was confirmed by an in vitro histamine release assay. The leukocytes from 23 patients (38%) released histamine to food antigens. Patients eliminated foodstuffs in a double-blind trial to correlate the in vitro histamine release to the development of oral ulcers. Only 30% of the patients had a decreased incidence of ulcers after eliminating foods which had induced in vitro histamine release. On rechallenge in the double-blind trial, 30% of the foods which caused histamine release also correlated to increased incidence of oral lesions. In eight patients ingestion of certain foodstuffs were correlated to oral ulceration by food diaries and elimination-rechallenge in an open-trial basis. However, dietary manipulation did not completely eliminate the ulceration in any of the patients. The results suggest that food sensitivity may play a minor role in the development of recurrent aphthous stomatitis.

E. Allergy To Laboratory Animals.

Skin tests and in vitro histamine release with 15 different allergens were used to evaluate a group of 130 patients seen in an employee allergy clinic. The allergens included extracts from pollens (ragweed, grasses, trees, weeds), mold, feathers, house dust, cat, dog, mouse, rat, rabbit, guinea pig and hamster. 68% of the patients worked with laboratory animals; 48% reacted to pollens and 46% to laboratory animals. With laboratory animal pelt allergens there was good correlation between the intradermal skin test (with 100 Protein Nitrogen Units (PNU)/ml) and the histamine release (with 1, 10 and 100 PNU/ml); leukocytes from 91% of the 4+ skin reactors released histamine. The laboratory animal-allergic individuals reacted by skin test and their leukocytes released histamine with the various laboratory animal pelt extracts (e.g., when the leukocytes were positive with mouse allergen, they were also positive with rabbit, guinea pig, hamster or rat allergens in 67%, 69%, 82% and 92% of the tests respectively). There was significant correlation by the χ^2 -test to reactions with different laboratory animals. There was also correlation with cat and dog allergen. Only half of the laboratory animal-allergic individuals were also reactive to pollens. Therefore, non-pollen-allergic individuals also may develop sensitivity to laboratory animals. However, pollen-allergic individuals are at higher risk. The highest risk is among patients who are sensitive to domestic animals, e.g. cats or dogs.

II. Significance to Biomedical Research And The Program Of NIDR.

The purpose of the project is to study the immunologic release of mediators such as histamine which represent the effector mechanisms by which IgE, allergens, or microbial cells may interact with leukocytes or serum to cause inflammation.

III. Proposed Course

Experiments will pursue further pathways and regulatory mechanisms of immunologically-induced histamine release.

IV. Publications

1. Ida, S., Hooks, J., Siraganian, R.P. and Notkins, A.L.: Enhancement of IgE-mediated histamine release from human basophils by immune-specific lymphokines. Clin. exp. Immunol. 41:380-387, 1980.
2. Wahn, U., Peters, T. Jr. and Siraganian, R.P.: Studies on the allergenic significance and structure of rat serum albumin. J. Immunol. 125:2544-2549, 1980.
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5. Siraganian, R.P. and Hook, W.A.: Histamine Release and Assay Method for the Study of Human Allergy. In Manual of Clinical Immunology 2nd Edition. (Editors) N.R. Rose and H. Friedman, American Society for Microbiology, Washington, D.C. p. 808-821, 1980.
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7. Crews, F.T., Morita, Y., McGivney, A., Hirata, F., Siraganian, R.P. and Axelrod, J: IgE-mediated histamine release in rat basophilic leukemia cells: Receptor activation, phospholipid, methylation, Ca^{2+} flux and release of arachidonic acid. Arch. Biochem. Biophys. (In press).
8. McGivney, A., Morita, Y., Crews, F.T., Hirata, F., Axelrod, J. and Siraganian, R.P.: Phospholipase activation in the IgE-mediated and Ca^{2+} ionophore A23187 induced release of histamine from rat basophilic leukemia (RBL) cells. Arch. Biochem. Biophys. (In press).
9. McGivney, A., Crews, F.T., Hirata, F., Axelrod, J. and Siraganian, R.P.: Rat basophilic leukemia cell lines defective in phospholipid methyltransferase enzymes, Ca^{2+} influx and histamine release: Reconstitution by hybridization. Proc. Natl. Acad. Sci. U.S.A. (In press).
10. Siraganian, R.P., McGivney, A., Barsumian, E.L., Crews, F.T., Hirata, F. and Axelrod, J.: Use of variants of the rat basophilic leukemia cell lines for the study of histamine release. Fed. Proc. (In press).

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12. Siraganian, R.P.: The major allergens of mice. Allergologie (In press).
13. Hook, W.A. and Siraganian, R.P.: Skin test and leukocytes histamine release of patients with allergies to laboratory animals. Allergologie (In press).
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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00290-02 LMI
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Production of Hybridomas		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Siraganian, R. Fox, P.C. Axelrod, D. Hook, W.A. Sarfatti, D. Viswanathan, T. Basciano, L. Fischler, C. Berenstein, E.	Chief, Clinical Immunology Clinical Associate Clinical Associate Research Microbiologist Sr. Asst. Dental Surgeon Visiting Fellow Microbiologist Medical Technician Micro. Microbiologist	LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR LMI NIDR
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Microbiology and Immunology		
SECTION Clinical Immunology Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
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<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords)		
<p> <u>Hybridomas</u> are being produced which secrete <u>monoclonal antibodies</u> of defined antigen specificity and antibody subclass. Studies have demonstrated means for improving the yield of hybridomas. Using these methods a number of hybridomas have been produced including anti-DNP IgE, anti <u>Actinomyces viscosus</u>, anti-Cytophaga sp, anti-lymphokines (IL 1 and IL 2), anti-Fc_E receptor of mast cells, anti-human IgE, and anti-idiotypic. These monoclonal antibodies are being utilized in a number of biochemical and biological studies. </p>		

I. Objective

The aim of this project is the production of hybridomas secreting monoclonal antibodies of defined specificity. These hybridomas are being developed and purified for further studies utilizing sensitive in vitro assays and cell culture techniques.

II. Project Description

A. Techniques For Enhancing The Yield Of Antigen-Specific Hybridomas.

Two techniques were developed to enhance the frequency of antigen-specific hybridomas by enriching for antibody precursor or producing lymphocytes prior to cell fusion. Spleen cells from immunized animals were either: 1) cultured in vitro for four days in the presence of the immunizing antigen; or 2) transferred into x-irradiated syngeneic recipients followed by an in vivo antigen boost four days prior to their use in cell fusion. Both procedures decrease the total number of cells available for hybridization, but increase the percentage of antigen-specific antibody-secreting clones following cell fusion. In a series of 65 hybridizations a ~50-fold increase in the number of antigen-specific clones per 10^6 cells fused is observed following these treatments.

B. Production Of anti-Cytophaga Hybridomas.

Oral Cytophaga species attach to the cementum surface of teeth. Monoclonal antibodies (hybridomas) directed against these organisms could be used to study the mechanism of this attachment. Cytophaga sp. strain NS1001, a filamentous, gram negative, gliding, non CO_2 requiring bacteria, was isolated from subgingival plaque of patients with destructive periodontitis. Osborne-Mendel strain rats were immunized by placing whole formalinized bacteria in drinking water for three consecutive days at monthly intervals or by injection of the organism in complete Freund's adjuvant. The presence of specific serum antibodies was determined by a modified enzyme-linked immunosorbent assay (ELISA) utilizing as antigen outer membranes of NS1001 cells harvested by centrifugation. After three exposures, serum antibody was detected at a titer of $1:10^3$. Single cell suspensions were made of the spleens and 50×10^6 cells were injected intravenously into syngeneic recipients x-irradiated 24 hours previously with 500 Rads. Following cell transfer, the recipients were boosted by the intraperitoneal injection of $\sim 10^{10}$ whole formalinized Cytophaga sp. cells. Six days later spleen cells from the recipients were fused with the X63-Ag8.653 nonsecreting murine plasmacytoma using the polyethylene glycol method. Culture supernatants were tested 14 and 21 days after hybridization. Out of 168 wells, 34 showed cell growth and 23 had specific anti-Cytophaga sp. antibody. These positive cultures were expanded, cloned and screened to select hybridomas secreting monoclonal antibodies. These antibodies will be used to study the mechanism of adherence of the organism to the tooth surface.

C. Monoclonal Antibodies To Actinomyces viscosus T14V.

Nine monoclonal antibodies were produced which reacted with only one of two immunoelectrophoretically distinct fimbrial components on Actinomyces viscosus T14V. The fibrillar morphology of this component was revealed by the immunoelectronmicroscopic examination of bacteria incubated with the monoclonal antibodies. The lectin activity associated with these structures was detected by cross-linking the isolated fimbriae with the monoclonal antibodies to form immune complexes with lactose-inhibitable agglutinating activity for neuraminidase-treated human erythrocytes. Further studies with 19 human strains of A. viscosus and A. naeslundii revealed differences in the fine specificity of each antibody and associated the lactose-inhibitable lectins on these bacteria with fimbriae which are antigenically related to those of T14V. Therefore, a cell-associated lectin activity which mediates lactose-inhibitable adherence of Actinomyces viscosus T14V has been localized to a distinct fimbrial component by the use of monoclonal antibodies.

D. A Solid-Phase Histamine Release From Basophils; Use for detecting IgE-Secreting Hybridomas.

A rapid and simple in vitro method for detecting IgE-producing hybridomas was developed. The technique is based on the fact that rat basophilic leukemia cells (RBL-2H3) have high affinity receptors for IgE, grow firmly attached on plastic surfaces and can be activated by anti-IgE or antigen to release histamine and serotonin. Supernatants from fused cells were tested for IgE-activity by their capacity to sensitize the RBL-2H3 cells for IgE-mediated histamine release. The method allows for rapid screening of large numbers of samples. IgE-producing hybridomas were obtained by the fusion of spleen cells from mice parasitized with Nippostrongylus brasiliensis with a plasmacytoma cell line. The IgE produced by one of these clones has been purified and characterized. Utilizing this technique with spleen cells from DNP-immunized mice we have been successful in producing two anti-DNP monoclonal antibodies of the IgE immunoglobulin class.

E. Monoclonal Antibodies To Human IgE.

Anti-human IgE hybridomas were prepared by immunizing BALB/c mice with the purified human IgE myeloma protein "PS". Splenocytes were hybridized with the nonsecreting mouse myeloma cell line X63-Ag8-653. Cells producing antibody to the "PS" myeloma were expanded and cloned. Mouse ascites were produced by injection of cloned hybrid cells having anti-IgE activity. Culture supernatants and ascites containing anti-IgE antibody were purified by ammonium sulfate precipitation followed by DEAE chromatography and were shown to be of the IgG class by immunodiffusion. They were quantitated in vitro by 1) histamine release (HR) from normal human leukocytes; 2) enzyme-linked immunosorbent assay (ELISA) using myeloma protein "PS"; and 3) radioimmunoassay (RIA) with labeled human IgE myeloma "ND". None of these hybridomas react with pooled human IgG. The table shows that among nine hybridomas obtained, three different patterns of reactivity were found.

Culture		Anti-IgE Activity By:		
Type	Number	HR	ELISA	RIA
1	4	-	+	-
2	4	+	+	+
3	1	-	+	+

Type 1 are anti-idiotypic antibodies; type 2 are against common IgE determinants and type 3 are directed toward determinants hidden when IgE is on the basophil surface. Therefore, antibodies directed toward distinct portions of the IgE molecule were produced.

F. Monoclonal Antibodies To The Fc_{ϵ} Receptor On Rat Basophilic Leukemia Cells.

Monoclonal antibodies of mouse origin to the Fc_{ϵ} -receptor of rat basophilic leukemia (RBL-2H3) cells were isolated. Splenocytes from BALB/c mice repeatedly immunized with RBL cells were hybridized with the nonsecreting mouse myeloma cell line X63-Ag8-653. Anti- Fc_{ϵ} -receptor antibody producing hybrids were selected by the capacity of the supernatants to inhibit RBL cell sensitization with IgE for antigen-induced histamine release. A large number of anti-cell surface hybridomas were negative by this assay. Positive cultures were cloned, selected and injected into BALB/c mice for the production of ascitic fluid. The antibodies were purified by ammonium sulfate precipitation and DEAE chromatography. The anti- Fc_{ϵ} -receptor antibodies were found to be of the IgG_1 subclass. Purified anti- Fc_{ϵ} -receptor antibody at 1.3 $\mu g/ml$ inhibited by 50% the binding of 0.3 $\mu g/ml$ ^{125}I -labeled rat IgE to 2×10^6 RBL cells at 100 min; and at 2 $\mu g/ml$ inhibited by 50% sensitization of RBL cells for IgE-mediated histamine release. The Fab monomer also inhibited IgE-mediated histamine release and the binding of ^{125}I -labeled rat IgE to RBL cells. The anti- Fc_{ϵ} -receptor antibody did not release histamine (release <5%) when added either alone or followed by rabbit anti-mouse immunoglobulin. Therefore, the hybridoma antibody binds to a site in the IgE Fc_{ϵ} -receptor that cannot mediate histamine release. Monoclonal anti-receptor ϵ antibodies can be used to study the different functional domains of the IgE receptor.

G. Monoclonal Antibodies To An Idiotypic.

Studies of how the immune response is regulated have focused on the phenomenon of idiotypes on antibodies and receptors. These structures act as specific markers of antibody producing cells which are recognized by the cellular components of the immune system (T-cells predominantly) leading to immune homeostasis. The control of immunoglobulin E (IgE) synthesis is of particular interest since IgE is an obligate component of the allergic reaction. We are using a particular IgE myeloma product, SpE IV 7 IF, which is specific for DNP (2,4 dinitrophenyl group). This anti-DNP reactivity allows us to purify the antibody on affinity columns to assure a monospecific antigen. This system is particularly valuable because the immune response to DNP is well characterized for other immunoglobulin classes.

Rats were immunized with the anti-DNP IgE hybridoma and following adoptive transfer as described above were hybridized. Both anti-idiotypic and anti-mouse IgE hybridoma were produced; the anti-idiotypic's reaction with the immunizing antigen is inhibited by the DNP hapten. The antibodies are being purified for in vivo and in vitro studies.

H. Monoclonal Antibodies Against Interleukins.

The generation of monoclonal antibodies against Interleukin 1 (IL 1; the lymphocyte activating factor) and Interleukin 2 (IL 2; the T cell growth factor) is of interest. Macrophage-derived IL 1 in conjunction with a mitogen or antigen activates T cells to produce IL 2. Thus, these mediators act as amplifying signals in the afferent limb of immunity. IL 1 and IL 2 have a number of biologically similar effects; therefore, antibodies might be helpful in dissecting the actions of these mediators as well as in affinity purification of these factors. Partially purified IL 1 and IL 2 were used to immunize BALB/c mice and following adoptive transfer the spleen cells were used for hybridization. The positive culture supernatants were expanded, cloned and transferred to mice for the production of antibodies in ascites. Six different monoclonal antibodies to IL 2 were produced and another six to IL 1. The monoclonal antibodies against the interleukins should provide an accurate tool for the study of the regulatory role of these mediators. The antibodies should also provide a powerful tool for the purification of IL 1 and IL 2 and for their use in other biochemical and biological assays.

III. Significance

Hybridomas have been produced successfully to a number of different antigens. The monoclonal nature of these antibodies makes them a unique tool for immunological and biochemical studies. The hybridomas produced in these studies will be used to study interactions involved in the control and evolution of the inflammatory response.

IV. Proposed Course

Experiments will continue to further purify and define existing hybridomas and produce new hybridomas of unique antigen specificities or antibody subclasses.

V. Publications

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2. Fox, P.C. and Oppenheim, J.J.: Cell-Mediated Immunity, in Textbook of Microbiology with Dental Applications. Harper and Row, (In press).

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ANNUAL REPORT
Laboratory of Biological Structure
National Institute of Dental Research

The research efforts of the Laboratory of Biological Structure are focused on the elucidation of the structural, chemical and functional characteristics of the hard and soft tissues of the oral cavity. Of the four sections comprising the laboratory, the activities of three are directed toward skeletal and dental tissues, with the objectives of understanding their normal growth and development, characterizing their synthetic products, and determining the physicochemical and biological mechanisms of mineralization. The pursuit of these common goals through widely divergent approaches forms the basis for fruitful collaborative efforts between these groups. While the program of the fourth group deals primarily with secretory tissues, its morphological orientation also lends itself to collaborative studies with the other research groups. As is evident from the individual project reports, LBS thus has the capacity to deal with significant biological problems employing an integrated investigative approach.

Skeletal Matrix Biochemistry Section

The Skeletal Matrix Biochemistry Section of LBS has made a number of advances in our knowledge of the non-collagenous matrix proteins of enamel and bone during the past year. Characterization of the amelogenin proteins of developing enamel of several species revealed a range of molecular sizes, from 5,000 to 40,000 daltons. Combined data from in vivo biosynthetic studies, amino acid compositions, and changes in molecular size with increasing enamel maturation suggest that the 40,000 dalton amelogenin is the precursor for all of the smaller size amelogenins. These smaller molecules appear to be produced by a discrete, non-random degradative cascade, and are eventually completely lost following tooth eruption. Protein chemistry and sequence data have revealed that the amelogenins are highly amidated, apolar molecules and that the amino acid sequence of the 5,200 dalton, tyrosine-rich polypeptide is considerably different than that reported in the literature for this molecule. The enamelines, the other loss of enamel matrix proteins, are tightly bound to the enamel crystallites. They also undergo a degradative cascade during maturation, but at a slower rate than the amelogenins, so that small amounts of low molecular weight (2,500-3,000 daltons) enamelin proteins are present in fully mature enamel. In human enamel a portion of these molecules have a high phosphate content, are so tightly bound to the crystal surfaces that the crystals are rendered impervious to dissolution by EDTA or dilute acids. Ultrastructural studies employing differential extraction with guanidine-HCl have demonstrated that the organic envelopes observed around enamel crystallites consist primarily of enamelines, and that the amelogenins are mainly present in the intercrystalline spaces. In vitro studies of protein free enamel crystals and synthetic hydroxyapatite combined with purified amelogenins and enamelines have shown that both proteins will bind to and form envelopes around the mineral crystals.

Studies of the matrix proteins of fetal calf bone have demonstrated that 85% of the non-collagenous proteins is comprised of six molecular constituents, three of which are serum derived, along with three newly-described tissue specific proteins. One of these proteins, with a molecular weight of 32,000 daltons, has been shown to bind strongly to both collagen and hydroxyapatite, and to nucleate mineral phase deposition from metastable balanced salt solutions.

Indirect immunofluorescent studies have localized this protein to mineralizing bone trabeculae; it appears to be absent from other tissues. Based on its tissue source, bifunctional nature, and potential role in active mineralization, this protein was named osteonectin. Additional studies have investigated the nature of the proteoglycan of bone matrix and shown it to be a much smaller molecule than the major cartilage proteoglycan. It is chemically similar to the proteoglycans of sclera, cornea, skin and arterial tissue, and it cross-reacts immunologically with antisera against the minor, low buoyant density proteoglycans of cartilage.

Bone Cell Biology Section

The Bone Cell Biology Section is concerned with the differentiation, growth and mineralization of endochondral bone. The experimental model used for most of the section's work takes advantage of the bone-inducing properties of subcutaneously implanted demineralized bone matrix powder. The various developmental stages occur in a defined temporal sequence, which provides a useful assay system for studies of the effects of various nutritional, hormonal and pharmacological treatments on cartilage, bone and bone marrow formation. Additionally, characterization of many of the specific events involved in cartilage and bone differentiation are possible. This year, for example, studies on the role of fibronectin in cell attachment, proliferation and differentiation were continued, as were studies on the appearance of one of the major non-collagenous bone proteins, the bone γ -carboxyglutamic acid-containing protein. Similarly, changes in specific enzymes of collagen synthesis and polyamine synthesis were followed. Finally, the appearance and localization of various degradative enzymes were investigated, particularly those involved in chondrolysis and bone remodeling.

These studies, along with those reported in previous years, have contributed significant insights into the biochemistry and physiology of cartilage and bone development. Much of this data could not have been as readily obtained without the use of the bone induction model system. The most fundamental question, though, remains: what are the specific substances present in the demineralized bone powder which initiate the entire sequence of endochondral bone formation? A major step was taken this year with the demonstration that treatment of the demineralized bone powder with dissociative solvents results in the extraction of the inductive molecules, and that reconstitution of the inductive properties can be achieved by recombining the collagenous residue with the extracted molecules. Implantation of this reconstituted matrix material results in bone induction equal to or greater than that achieved with non-extracted bone powder. The next steps are to purify and characterize the extracted molecules, and to assay their ability to induce bone by recombining them with the inactive collagenous residue. These results suggest that in the near future, the isolation and characterization of one or more molecules involved in the inductive process may be forthcoming.

Mineral Chemistry and Structure Section

The efforts of this section continue to focus on the physical and chemical characteristics of calcium phosphate compounds of biological interest. An important finding this year was achieved using Extended X-ray Absorption Fine

Structure (EXAFS) analysis at the Stanford Synchrotron Radiation Laboratory. Using this technique, amorphous calcium phosphate preparations were shown to be truly non-crystalline in structure, rather than microcrystalline as some investigators have suggested. Thus, amorphous calcium phosphate is most likely a distinct mineral entity.

Additional studies undertaken by the Mineral Chemistry and Structure Section have dealt with analogues of intracellular calcium precipitation systems. The potential calcium accumulating properties of matrix vesicles were explored in a system consisting of two aqueous phases separated by an organic phase containing an ionophore. Ca^{++} was transported by the ionophore from one aqueous phase to the other, through the organic phase, if K^+ was present in the second aqueous compartment to act as an exchange ion. Sufficient Ca^{++} could be transported to precipitate with phosphate in the second compartment as amorphous calcium phosphate. This study demonstrates the feasibility of calcium accumulation by matrix vesicles, although the biological occurrence of such a phenomenon has yet to be described. The dense bodies of platelets, which bind high levels of biogenic amines, contain a core of calcium-adenosine phosphate-pyrophosphate. Studies of synthetic analogues have provided a potential mechanism to account for the ability of the dense bodies to bind such high levels of amine. Neutral serotonin molecules in the cytosol readily penetrate the membrane of the dense body. Once inside, they are protonated by an acid phosphate group and are unable to diffuse out of the dense body. Net retention of the serotonin is achieved because the high concentrations of transferable protons in the dense body far exceeds that found in the cytosol. These synthetic systems continue to prove useful in interpreting physico-chemical phenomena in biological mineralization.

In line with the interest of the section in studying relevant biological phenomena, Dr. John L. Meyer has begun a Foreign Work/Study assignment in the laboratory of Dr. Herbert Fleisch at the Pathophysiology Institute of the University of Bern, Switzerland. The emphasis of his training will be on techniques suited to the study of the role and function of physiologically active inhibitors of calcification.

Experimental Morphology Section

The investigations of this section have continued to focus on secretory tissues and events related to exocrine secretory processes. Stimulation of exocrine gland secretion by adrenergic or cholinergic secretagogues either in vivo or in vitro results in a number of morphological and biochemical changes related to exocytosis and the eventual resynthesis of secretory proteins. The initial event in stimulation is the interaction of the agonist with specific receptor molecules on the plasma membrane. In the parotid gland, the signal for secretion is transmitted through activation of adenylate cyclase and changes in the activity of cyclic AMP-dependent protein kinases. During the past year we have determined that the parotid protein kinase is primarily organelle associated rather than free in the cytoplasm, and β -adrenergic stimulation increased the specific activity of the extranuclear particulate enzyme. Further, stimulation caused a redistribution of the regulatory subunits of the enzyme, such that the type I isozyme appeared in the extranuclear fractions and the ratio of type I to type II on the membranes of a purified secretory granule fraction was increased. These findings

suggest that phosphorylative modifications, probably of specific proteins, are important events in the initiation of exocrine secretion.

Previous studies demonstrated that exocrine cells also respond to secretory stimulation by increased endocytosis from their basal and lateral surfaces. The endocytosed material initially accumulates in a separate lysosomal system in the basal cytoplasm of the cells. Further characterization of this process has shown that these lysosomes contain several hydrolytic enzymes, but not acid phosphatase. Additionally, different molecular tracers, including both positively and negatively charged molecules, are internalized by similar mechanisms and sequestered in the same intracellular compartments.

An additional response of the salivary glands and other exocrine tissues to secretory stimulation appears to be an alteration in the permeability of the junctional complexes between adjacent epithelial cells. Under normal conditions the tight junctions prevent passage of macromolecules between the lumen and the intercellular spaces. Stimulation of the parotid gland with isoproterenol increases the permeability of the tight junctions, so that molecules of at least 40,000 daltons can penetrate from the lumen to the intercellular spaces. Preliminary freeze-fracture studies indicate that the structure of the tight junctions is disrupted at 30 minutes after isoproterenol. Studies in progress are utilizing retrogradely injected tracers to characterize the permeability characteristics of the altered junctions, and assessing the potential for transfer of blood-borne substances to the saliva.

Laboratory of Biological Structure
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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00074-09 LBS
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Protein-Crystal Relationships in Mineralized Tissues		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Termine, J.D. Conn, K.M. Kaplan, K.A. Obermeier, C.I. Arnesen, S.J. Belcourt, A.B. Fincham, A.G. Whitson, S.W. Youmans, P.A. DeGraff, B.A. Floyd, S.W. Nylen, M.U.	Research Chemist Research Chemist Biological Aid (Biochem.) Biological Aid (Biochem.) Biological Aid (Biochem.) Expert Visiting Scientist Guest Worker Secretary (steno) Purchasing Agent Photographer (laboratory) Director, IRP	LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR IRP NIDR
Continued on next page.		
COOPERATING UNITS (if any) 1) Dr. W.T. Butler, UAB, Inst. of Dental Res.; 2) Dr. H.C. Slavkin, USC, School of Dentistry.		
LAB/BRANCH Laboratory of Biological Structure		
SECTION Skeletal Matrix Biochemistry Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205.		
TOTAL MANYEARS: 5.13	PROFESSIONAL: 3.05	OTHER: 2.08
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The <u>biochemical</u> and <u>biophysical properties</u> of developing skeletal and dental tissue proteins are being studied by several techniques. <u>Dentin</u> , <u>bone</u> and <u>enamel matrix proteins</u> are also investigated as to their functional and structural influences on active <u>mineralization</u> in biological systems. Special emphasis is placed on <u>phosphoprotein</u> and <u>glycoprotein biochemistry</u> in these hard tissue matrix studies.		

Continuation page: Names, Laboratory and Institute Affiliations....

Yanagisawa, R.	Visiting Fellow	LBS NIDR
Martin, G.R.	Chief, LDBA	LDBA NIDR
Kleinman, H.K.	Research Chemist	LDBA NIDR
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Yanagishita, M.	Special Expert	LB NIDR

1. Project Description:

The extracellular matrix proteins of the bones and teeth are key elements in the structure and metabolism of these tissues. The goal of this project is to study matrix proteins specific to each mineralizing skeletal tissue in order to understand their molecular structure and biological function.

Our approach to the problems and difficulties posed by experimentation with hard tissue proteins is as follows: (1) We employ procedures carefully designed to minimize artefacts due to proteolysis and/or aggregation of matrix constituents; (2) we use an extraction scheme that differentiates proteins on their selective affinity for apatite mineral, thus concentrating those constituents vital to the unique mineralization function of skeletal tissues; (3) we study fetal or neonatal tissue at progressive stages of development to sort out the sequence of biochemical events associated with bone and tooth formation; and (4) we utilize a number of novel biochemical separation and characterization systems constructed specifically to cope with the unusual protein chemistry often encountered in the study of noncollagenous skeletal matrix constituents.

The major noncollagenous elements of the dentin extracellular matrix are highly phosphorylated proteins called phosphophoryns. We reported earlier that we purified the fetal bovine phosphophoryn and found it to be a glycosylated phosphoprotein considerably larger in size and different in composition than previously believed. Recently, we found several species-related differences in dentin phosphophoryn biochemistry. For example, the fetal bovine dentin molecule is 50% larger in molecular size and significantly different in amino acid composition than the phosphophoryns found in rodent tooth germ dentin. We are currently investigating the fetal human phosphophoryn molecule. As we described earlier, phosphophoryns modulate apatite crystallization and type I collagen fibrillogenesis in vitro, both in a calcium-dependent fashion. Thus, phosphophoryns, which comprise over one-half of the noncollagenous protein of developing dentin, may well play a role in the internal molecular architecture and mineralization pattern of this tissue. As such, they serve as an excellent model for matrix-mediated mineralization processes in other mammalian tissues.

We reported earlier that the experimental approach outlined above led to our discovery that the extracellular matrix of developing enamel consists of two biochemically distinct protein types. One of these is a proline-rich class (the amelogenins) that is hydrophobic in character and located, for the most part, between growing enamel apatite crystallites. This class comprises 90% of the secretory phase enamel matrix but is completely removed from the tissue with progressive enamel maturation. The second enamel protein class (the enamelines) consists of sialic acid-rich glycoproteins, acidic in character and tightly associated with surfaces of the growing enamel apatite crystallites. Recently, we found the enamelines to comprise the chemical source of that fraction of the developing enamel matrix that persists in the fully formed, erupted tooth. Both fetal enamel matrix protein types undergo extensive maturation-linked biochemical changes, alterations investigated in considerable detail this past year.

We studied the molecular species of amelogenin proteins present in developing enamel from cow, pig, sheep, hamster and human teeth. In each species, the amelogenin complex existed as a consistent set of similar proteins ranging in size from 5,000 to 40,000 daltons. For example, fetal bovine enamel contains: small amounts of 40,000 dalton amelogenins, probable precursors of all the remaining amelogenin proteins of lower molecular weight; larger quantities of a main secretory phase amelogenin complex at 27,000 daltons; several intermediates at 21,500, 15,000, and 12,500 daltons; and variable amounts (depending on stage of maturation) of amelogenin polypeptides at 8,200, 7,800, 6,500 and 5,200 daltons. Each species contained two specific low molecular weight (5,000-7,000 dalton) amelogenin polypeptides, one rich in leucine and the other in tyrosine, whose relative proportions in the total matrix increased with progressive enamel maturation. This pattern of a coupled decrease in the proportion of higher molecular weight amelogenin proteins with a corresponding increase in specific, low molecular weight amelogenin polypeptides (concomitant with increasing mineralization) was a consistent feature of enamel development, even within sections from single bovine molar teeth. Thus, the amelogenin fraction of developing enamel is removed from the tissue (as mineralization increases) in a discrete, degradative cascade where larger molecules are processed to specific smaller ones prior to their eventual disappearance following tooth eruption. This suggests a concise, non-random mechanism of amelogenin degradation, perhaps by tissue-specific enzymes as yet not completely characterized.

Preliminary data on the processing of enamelin proteins during progressive tooth mineralization suggest that this fraction of the developing enamel matrix also undergoes controlled or discrete degradation with tooth maturation, but at a slower rate than that observed for the amelogenin complex. This difference is probably related to the close association of the enamelin proteins with the tooth enamel apatite, perhaps making them less susceptible to proteolytic breakdown than the intercrystalline amelogenin matrix complex. Drs. T. Yanagisawa and M.U. Nylen demonstrated that while both amelogenins and enamelins can interact with deproteinized enamel apatite to form a protein sheath or coat about individual crystallite surfaces, quantitation of the native protein coat about in situ enamel crystallites (before and after removal of tissue amelogenin proteins) suggests that, in vivo, growing enamel crystallites are enveloped by a protein coat consisting primarily of matrix enamelins. The enamelin proteins that survive maturation-linked degradation and form the "matrix" of adult human teeth were low molecular weight (2,500-3,000 dalton) glycoproteins. We found a portion of these small adult enamelins to contain higher than normal levels of organic phosphate. This latter fraction was tightly bound to enamel apatite, rendering its associated mineral fraction impervious to dissolution by EDTA or dilute acids. This finding may be of some significance to the variable caries resistance of sound enamel surfaces.

In vitro studies of enamel matrix biosynthesis from organ cultures of neonatal hamster molar tooth germs (conducted in collaboration with Dr. H.C. Slavkin, USC School of Dentistry), supported the chemical findings described above. In culture, the hamster enamel organ synthesizes both amelogenin and enamelin proteins. Pulse-chase experiments showed that amelogenin proteins were processed from an initially secreted product of ~40,000 daltons through a 25,000 dalton amelogenin complex which was then rapidly broken down to the smaller amelogenin polypeptides described above. In contrast, the newly synthesized

matrix enamelin fraction was much more stable, showing different kinetics of biosynthesis and degradation vs. that observed for the amelogenins over the time frame studied. These data support the idea that amelogenin and enamelin proteins are separate and distinct gene products of secretory ameloblast cells.

Finally, we are conducting careful protein chemistry studies of chromatographically and electrophoretically homogeneous amelogenin molecules. These experiments include primary structure sequence determinations (in collaboration with Dr. W.T. Butler, UAB Institute of Dental Research) of specific amelogenin polypeptides. In brief, these studies have revealed the following new information: 1) the amelogenin proteins, both as a class and individually, are highly amidated, apolar molecules having hydrophobic indices as high as 75-80%, making them one of the most apolar protein groups in mammalian biology; 2) the 27,000 dalton amelogenin complex is processed, at least in part, to a 21,500 dalton intermediate by cleavage of its amino terminal (5,200 dalton) tyrosine-rich polypeptide; and 3) the amino acid sequence and phosphorous content of this tyrosine-rich polypeptide (called E-4) is substantially different from that thought earlier by other investigators. No doubt, other surprises will result from extensions of these protein chemistry studies in view of the unusual composition and unique chemical properties of the amelogenin proteins.

Type I collagen accounts for ~90% of the organic content of bone. However, comparatively little was known up to now, of the remaining noncollagenous portion of the developing bone extracellular matrix. Serum proteins, particularly the α_2 -HS-glycoprotein and albumin, were found to accumulate in bone tissue probably binding to the mineral phase. Ground substance (proteoglycans and glycosaminoglycans) was known to be present in bone and different from that of cartilage, but never chemically characterized. Recently, the α -carboxyglutamic acid-containing protein, osteocalcin, has been identified as a bone constituent and studied extensively. However, this low molecular weight (5,800 dalton) polypeptide is not present at appreciable levels during active bone formation and is thought to be involved in the maintenance or turnover of bone rather than in active osteogenesis. Various phospho- or glycoproteins have been suggested previously as bone constituents, but rarely studied in detail. Consequently, the role of individual matrix proteins in bone metabolism and disease processes has not yet been elucidated, as it has been in other tissues, primarily due to a scarcity of detailed information available about such bone-specific noncollagenous molecules.

When we applied our extraction and fractionation procedures to fetal calf bone, we found that approximately 80-85% of the noncollagenous matrix was comprised of only six molecular components. These were the serum-derived α_2 -HS-glycoprotein (20% of the bone noncollagenous protein), osteocalcin (15%), the bone proteoglycan (5%), and three newly-discovered, phosphate-containing proteins at molecular weights of 62,000 (10%), 32,000 (25%) and 24,000 (7%). The remaining 15-20% of the fetal bone noncollagenous matrix was found to be rich in serum and cell-derived constituents. The special precautions taken to avoid aggregation and/or breakdown of tissue protein were particularly key to our success in this study. For example, we found considerable neutral and acidic protease activity in fetal bone extracts, factors that, if not sufficiently countered, could drastically alter the results obtained.

With progressive fetal age, osteocalcin levels rose as the relative proportion of bone-incorporated α_2 -HS-glycoprotein declined, probably reflecting the relative affinities of these two proteins for bone mineral surfaces. Conversely, the three new phosphate containing proteins at 24,000, 32,000 and 62,000 daltons remained constant throughout fetal bone development, probably reflecting a more integral role for these proteins in bone structure and/or function. These three proteins, which could only be extracted from bone upon dissolution of the mineral phase, were concentrated in tissue areas rich in actively mineralizing bone trabeculae. We purified these proteins to homogeneity and found the 32,000 and 62,000 dalton molecules to contain both carbohydrate (e.g., glucosamine, galactosamine and sialic acid) and organic phosphate. The 24,000 dalton protein was devoid of carbohydrate but contained both organic phosphate and hydroxyproline (2.7% of the amino acid residues). None of these components were derived from serum (immunological criteria) or from collagen/procollagen (enzymatic and chemical data). Thus, they are excellent candidates for bone-specific structural and/or biological functions.

The most interesting of the fetal bone matrix constituents was the 32,000 dalton phosphate-containing glycoprotein. Characterization of the biological properties of this protein was carried out in collaboration with Drs. G.R. Martin and H.K. Kleinman, LDBA, NIDR. This protein had the greatest affinity of all the bone proteins for both hydroxyapatite and collagen. It was selectively adsorbed by apatite even in 4M guanidine HCl and on gelatin affinity columns at physiological pH and ionic strength. Thus, we named this protein osteonectin on the basis of its potential to bind or link the bone mineral and collagen phases. Additional experiments further supported this idea. When osteonectin was bound to insolubilized type I collagen (obtained from non-mineralizing tissue sources), the resultant complex selectively bound synthetic apatite crystals and free calcium ions. Prior treatment of the collagen with fibronectin or of the osteonectin with antibody to that molecule effectively blocked the binding. These data showed that osteonectin is a bi-functional protein with separate domains capable of binding to either collagen or mineral species. In addition, the osteonectin-collagen complexes nucleated mineral phase deposition from metastable balanced salt solutions, further illustrating the potential significance of this protein to the bone mineralization process. Antibodies to osteonectin cross-reacted with bone and, to a lesser extent dentin, but not with other fetal calf tissues. The protein was localized by indirect immunofluorescence to mineralizing bone trabeculae in subperiosteal, metaphyseal and intramembranous bone and occurred at higher levels in the matrix than in the cells of bone. These studies suggest that osteonectin is a tissue-specific protein, perhaps involved in active mineralization in normal skeletal tissue.

Ongoing studies (done in collaboration with Drs. M. Yanagishita and J.H. Kimura, LB, NIDR) of the bone proteoglycan amply demonstrate its non-identity with the major proteoglycan species of cartilage. The data indicate that the fetal calf bone proteoglycan (derived from either unmineralized or fully mineralized bone tissue) is a small glycoconjugate of approximately 100,000-120,000

daltons to which are attached: a) about 10-12 oligosaccharide units (~1000-1500 daltons each) containing hexosamine and/or sialic acid; and b) two polydisperse glycosaminoglycan chains (ave. ~40,000 daltons each) composed of internal copolymers of both chondroitin and dermatan sulfate. The bone proteoglycan is immunologically distinct from the larger cartilage proteoglycans but does cross-react with antisera against the minor constituent, low buoyant density proteoglycans of that tissue. In addition, the fetal bone proteoglycan is chemically similar to proteoglycans found in sclera, cornea, skin and arterial tissue. Thus, further efforts along these lines should prove illuminating to the composite biochemistry of bone and other connective tissues.

Perturbances in mineral metabolism and other calcification diseases have always presented perplexing clinical difficulties in the various branches of dentistry and medicine. On a basic science level, it is almost impossible to cope with these pathologies in the absence of certitude as to the properties and functions of the extracellular matrix proteins differentiating each skeletal tissue type. Consequently, this research program will focus its future efforts on 1) identifying the individual noncollagenous matrix proteins specific to enamel, dentin and bone, 2) mapping out their internal molecular structure, and 3) unraveling their biogenesis, matrix localization and biological functions within their parent tissues.

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Fincham, A.G., Belcourt, A.B. and Termine, J.D.: Molecular composition of fetal bovine enamel matrix. In Veis, A. (Ed.): The Biology of Mineralized Connective Tissue Elsevier-North Holland, N.Y., (in press).

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00204-05 LBS
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Extracellular Matrix and Bone Differentiation		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Reddi, A.H.	Research Biologist	LBS NIDR
Kuberasampath, T.	Visiting Fellow	LBS NIDR
Wientroub, S.	Visiting Fellow	LBS NIDR
DeSimone, D.P.	Postdoctoral Fellow	LBS NIDR
Chen, G.T.	Chemist	LBS NIDR
Oldach, D.W.	Biological Aid	LBS NIDR
Whall, J.	Biological Aid	LBS NIDR
Trimble, F.	Biological Aid	LBS NIDR
Youmans, P.A.	Secretary (steno)	LBS NIDR
DeGraff, B.A.	Purchasing Agent	LBS NIDR
Floyd, S.W.	Photographer (laboratory)	LBS NIDR
Rattley, C.	Student Trainee (BIO SCI)	LBS NIDR
Somerman, M.J.	Staff Fellow	DB NIDR
COOPERATING UNITS (if any) Dr. Klaus Kuettner, Rush Medical College, Chicago, IL.; Dr. R.E. Weiss, U. of Southern California; Dr. Paul Price, U. of California, San Diego.		
LAB/BRANCH Laboratory of Biological Structure		
SECTION Bone Cell Biology Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 6.02	PROFESSIONAL: 3.87	OTHER: 2.15
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The objective of this project is to investigate extracellular matrix-cell interactions employing an experimental system of matrix-induced endochondral bone differentiation. This experimental model further affords a method to undertake systematic studies on the biochemistry and physiology of endochondral bone formation. Subjects currently under investigation are: (1) the mechanism of action of <u>matrix components</u> in bone differentiation; (2) role of <u>fibronectin</u> in collagenous matrix-mesenchymal cell interaction; (3) biochemical mechanisms involved during <u>vascular invasion</u> of cartilage; (4) developmental appearance of <u>vitamin-K dependent bone γ-carboxyglutamic acid</u> containing protein; (5) changes in <u>polyamines</u> and RNA synthesis during matrix-induced cartilage, bone and bone marrow development; (6) changes in intracellular enzymes of <u>collagen biosynthesis</u> during endochondral bone development; (7) local influence of <u>somatostatin</u> on endochondral bone development; and (8) activity and distribution of <u>lysosomal enzymes</u> during bone and bone marrow development.		

1. Project Description:

Introduction and Background:

The origin and evolution of multicellular organisms were marked by the appearance and specialization of extracellular matrices. The extracellular matrix is predominantly composed of collagens, proteoglycans and glycoproteins. Of all the tissues in the body, only bone, cartilage, tendon and tooth exhibit vast expanses of extracellular matrix. While we know that all extracellular matrices are products of cellular biosynthetic activity, we know very little about the interactions and feedback between matrix and cells. Our studies have concentrated on the area of collagenous bone matrix-cell interactions.

We have developed a useful experimental method to investigate several aspects of endochondral bone differentiation. Subcutaneous transplantation of demineralized rat bone or tooth matrix results in induction of bone formation locally. The sequential cellular changes are (1) transient chemotaxis for leukocytes (days 1-2); (2) a more prolonged chemotaxis for fibroblasts (days 2-3); (3) cell proliferation (days 3-5); (4) chondrogenesis (days 5-7); (5) hypertrophy and calcification of cartilage (days 9-10); (6) osteogenesis and bone mineralization (days 11-14); (7) remodeling of the ossicle (days 14-18); (8) differentiation of hematopoietic bone marrow (days 18-24).

The induced bone and bone marrow persist in a functional state. The temporal sequence is highly reproducible and we have extensively studied the factors influencing the sequence. This experimental model is the mainstay of our work and affords a system to dissect the main events in endochondral bone formation.

Experimental Methods:

Diaphyseal shafts are prepared from adult rats by standard techniques. Pulverized matrix particles of uniform size are then demineralized prior to implantation. The usual repertoire of standard biochemical laboratory techniques such as density gradient centrifugation, column chromatography, gel electrophoresis and radioisotopic tracer methodology are extensively employed.

Mechanisms of Action of Extracellular Matrix Components Involved in Bone Induction:

The biochemical mechanisms underlying endochondral bone induction by demineralized bone matrix are not well understood. We have explored the potential of three dissociative extractants, 8M urea, 4M guanidine hydrochloride and 1.0% (w/v) sodium dodecyl sulfate (SDS) at pH 7.4, containing protease inhibitors, to solubilize putative inductive molecules in the bone matrix. Extraction of bone matrix with 8M urea with 1M NaCl, 4M guanidine hydrochloride and 1.0% SDS resulted in the loss of the bone inductive property. The solubilized extracts were then reconstituted with the residue of the extracted matrices by dialysis against water. The various matrices were bioassayed for bone inductive potential by quantitation of alkaline phosphatase activity and ⁴⁵Ca incorporation on day 12. The results showed that there was a complete recovery of biological activity after reconstitution of the residues with each of the three extracts of

4M guanidine, 8M urea and 1% (w/v) SDS. These results demonstrate the dissociative extraction and successful biological reconstitution of the bone inductive macromolecules in the extracellular matrix. Future experiments will focus on molecular characterization of the components and elucidation of their mode of action.

Role of Fibronectin During Collagenous Matrix-Mesenchymal Cell Interaction:

Fibronectin is a major cell surface glycoprotein which functions in vitro as a cell attachment factor for cell-substratum (generally collagen) interaction. The importance of fibronectin in in vivo collagenous matrix-mesenchymal cell interaction was investigated using purified antibodies to rat plasma fibronectin. Local injections of the purified antibodies apparently inhibited collagenous matrix-mesenchymal cell interaction by inhibiting the action of endogenous fibronectin. Anti-fibronectin treatment resulted in reduced cell proliferation as assessed by [³H] thymidine incorporation (59% reduction) and ornithine decarboxylase activity (66% reduction) and chondrogenesis as measured by proteoglycan synthesis (43% reduction). Neutralization of fibronectin's biological activity by antibodies also resulted in a qualitative change in the proteoglycan type synthesized. The physiological role of fibronectin in tissue morphogenesis appears to be the mediation of initial extracellular matrix-cell attachment.

Biochemical Mechanisms Involved during Vascular Invasion of Cartilage:

During endochondral ossification, the replacement of calcified cartilage by bone is accompanied by vascularization. Although vascularization is an important process in bone differentiation, the mechanisms of this neovascularization are incompletely understood. The invasion of capillaries during this process may be accompanied by the release of proteases which may be responsible for the dissolution of certain areas of the extracellular cartilage matrix, particularly the transverse septa. Whereas calcified cartilage undergoes vascularization, certain tissues, such as hyaline cartilage, are resistant to vascular invasion. It has been shown that this resistance may be partially mediated by protease inhibitors in the tissue, which seem to be one of the active components of the cartilage derived anti-invasion factor (AIF). We have examined the role of proteases and protease inhibitors during vascular invasion of cartilage, a step that appears to be a prerequisite for bone differentiation and mineralization.

Changes in the levels of lysozyme, patterns of glycosaminoglycans, and activities of proteases and protease inhibitors were studied during matrix-induced cartilage, bone, and bone marrow development. The morphological transitions were correlated with the biochemical parameters. There was a peak in lysozyme content on Day 3, during mesenchymal cell proliferation, followed by a decline during endochondral bone formation. The lysozyme levels increased again and attained maximal values during hematopoiesis on Day 21. Protease-inhibitory activity was maximal on Day 3 during mesenchymal cell proliferation and was apparently present as an enzyme-inhibitor complex. Vascularization and bone formation were accompanied by an increase in protease activity. Chondroitin-4-sulfate was the predominant glycosaminoglycan detected in the matrix-induced cartilage and bone.

Developmental Appearance of Bone γ -Carboxyglutamic Acid-containing Protein (BGP):

The bone γ -carboxyglutamic acid containing protein (BGP) is a vitamin K-dependent protein of unknown function. BGP is one of the most abundant non-collagenous bone proteins, accounting for over 20% of total non-collagenous proteins in the EDTA extract of bone. Despite recent advances in the chemistry of this protein its role in developing mineralized tissues is not known. Several mineralizing tissues have been analyzed for BGP in order to establish the temporal relationship between initial mineral deposition and the appearance of BGP. These studies demonstrate that the appearance of BGP in developing bone is not dependent on birth, as had been suggested in earlier studies of rat development, but rather on the prior deposition of bone mineral. In fetal human bone, the level of BGP (grams of BGP/mol of bone PO_4) rises from 5% of the adult level at 10 weeks gestational age to the adult level at 15 weeks. Thus, adult levels of BGP are reached in human bone shortly after the initial appearance of mineral and long before birth. In adolescent rats, which have overall levels of BGP in bone near the adult level, the appearance of BGP at the ends of growing bones and bone induced by implantation of demineralized bone matrix follows mineral deposition by approximately 2 weeks. The relative absence of BGP in initially deposited bone mineral and its subsequent appearance several days later may be related to the maturation of bone mineral to hydroxyapatite, a structure which binds BGP.

Changes in Polyamines and RNA Synthesis During Matrix-induced Cartilage, Bone and Bone Marrow Development:

Changes in the levels of putrescine, spermidine, and spermine and their biosynthetic enzymes, ornithine decarboxylase (ODC) and S-adenosylmethionine decarboxylase (SAM-decarboxylase) were studied during matrix-induced endochondral bone and bone marrow development. Ribonucleic acid (RNA) synthesis was studied by [^3H] uridine incorporation into an acid-precipitable fraction. ODC and SAM-decarboxylase activity exhibited similar peaks on Day 3 and on Days 8 and 9 after matrix implantation and were correlated with corresponding peaks of [^3H]-thymidine incorporation during proliferation of chondroprogenitor and osteoprogenitor cells, respectively. In contrast, an increase in SAM-decarboxylase but not ODC was observed during hematopoietic bone marrow formation while the incorporation of [^3H]thymidine in these cells remained high. The concentrations of all three polyamines were low on Day 1, rose to peak values during osteogenesis on Day 11 and declined thereafter. Putrescine, but not spermidine, also exhibited an earlier smaller but broad peak on Days 3-7 during mesenchymal cell proliferation and cartilage differentiation. Incorporation of [^3H]uridine into acid-precipitable material exhibited two peaks on Days 5 and 11 during early phases of chondrogenesis and osteogenesis. The peak levels of putrescine, spermidine and spermine on Day 11 coincided with increased RNA synthesis during osteogenesis. Autoradiographic localization of [^3H]thymidine indicated a stimulation of cell proliferation adjacent to matrix particles prior to chondrogenesis and osteogenesis. Osteogenic precursor cells tended to be in close apposition to chondrolytic foci on Day 11. These results reveal that ODC and polyamines can be used as convenient markers of proliferation of chondrogenic and osteogenic cells during bone differentiation.

Changes in Intracellular Enzymes of Collagen Biosynthesis During Endochondral Bone Development:

The biosynthesis of collagenous proteins involves several post-translational modifications prior to secretion of procollagen molecules into the extracellular space. These intracellular modifications include hydroxylation of prolyl residues to their trans-4-isomers and trans-3-isomers, hydroxylation of certain lysyl residues and glycosylation of hydroxylysyl residues. The activities of five intracellular enzymes of collagen biosynthesis were determined during cartilage and bone formation induced in rats by demineralized bone matrix. The five enzymes, prolyl 4-hydroxylase, prolyl 3-hydroxylase, lysyl hydroxylase, hydroxylysyl galactosyltransferase and galactosylhydroxylysyl glucosyltransferase, exhibited broadly parallel profiles, the activities rising steeply from day one to reach their highest values on day nine and decreasing gradually thereafter. The maximal enzyme activity correlated with the period of chondrogenesis and hypertrophic cartilage characterized by the synthesis of cartilage-specific type II collagen. Prolyl 4-hydroxylase was also studied in regard to its tissue distribution and cellular location using indirect immunofluorescence. The enzyme was mainly located in the mesenchymal cells on day three, in the chondrocytes and hypertrophic chondrocytes on days seven to nine, and in the osteoblasts on day eleven and thereafter.

Local Influence of Somatostatin on Endochondral Bone Development:

The matrix-induced endochondral bone forming system is amenable to a systematic study of the role of hormones and nutrition on bone differentiation. Previous studies have examined the role of growth hormone, thyroid stimulating hormone and insulin on this phenomenon. Somatostatin (SRIF = Somatotropin release inhibiting factor) is a tetradecapeptide of hypothalamic origin that has an inhibitory influence on release of pituitary growth hormone. The influence of somatostatin on discrete stages of collagenous matrix-induced endochondral bone formation has been investigated. Local injection of somatostatin, i.e., without any measurable systemic effect, resulted in a 75% reduction of cell proliferation as measured by [³H]thymidine incorporation and ornithine decarboxylase activities. The minimum effective inhibitory dose of somatostatin was 0.25 µg/day. Twice daily local injections of the hormone during cartilage formation also resulted in an inhibition but this was shown to be due to impaired cell proliferation rather than a direct effect of somatostatin on differentiation. Injection of somatostatin into developing bone tissue after the cartilage stage impaired osteogenesis, assessed by ⁴⁵Ca incorporation and alkaline phosphatase activity. Concurrent injections of insulin and somatostatin obliterated the inhibitory effect of the latter on cell proliferation. Somatostatin can locally regulate the proliferation and differentiation of chondroprogenitor and osteoprogenitor cells in vivo and may directly contribute to the regulation of bone growth by its ability to counteract the stimulatory effect of insulin.

We propose to investigate next the interrelationships between Vitamin D metabolites and somatomedins with respect to bone differentiation. The role of insulin-like growth factors and MSA is currently under experimental scrutiny.

Activity and Distribution of Lysosomal Enzymes During Bone and Bone Marrow Development:

The appearance of the lysosomal enzymes acid phosphatase, arylsulfatase, and β -glucuronidase was studied during endochondral bone and bone marrow formation induced by implantation of demineralized bone matrix. The activities of acid phosphatase and β -glucuronidase gradually increased from the stage of mesenchymal cell proliferation on day 3 onward to reach a peak on day 13, during maximal bone remodeling. However, arylsulfatase activity exhibited a sharp increase on day 9, associated with the onset of cartilage hypertrophy and chondrolysis. The peak of arylsulfatase activity was also attained on day 13. The activities of all three enzymes declined on day 15 but acid phosphatase again exhibited an increase during hematopoietic bone marrow differentiation on days 19-21. Histochemical and ultrastructural studies revealed intense lysosomal enzyme activity in macrophage-like cells on day 7 and thereafter. During chondrolysis and bone remodeling, these cells were present in a perivascular location. Osteoclasts also exhibited strong reactivity for the lysosomal enzymes. Due to its characteristic temporal appearance during development of endochondral bone, arylsulfatase may be used as a marker enzyme for chondrolysis and bone resorption.

Significance to Dental and Medical Research:

A detailed knowledge of bone induction by extracellular collagenous bone matrix has immense implications for fracture healing and other orthopedic diseases, and in the realm of oral implants. These studies may also lead to an increased knowledge of the role of local factors governing bone formation and remodeling. In cancer, impaired matrix-cell interactions lead to metastases. Our experimental model represents a prototype for studying matrix-cell interactions and may shed light on the mechanisms involved in normal physiology and in pathogenesis of a variety of metabolic disorders afflicting the skeletal system.

Proposed Future Course of the Project:

The current studies on the mechanism of bone induction by bone matrix components will continue with full vigor. We propose to employ monoclonal antibodies to matrix components to dissect the molecular events in the early stages of bone induction. Future plans include the chemical characterization of molecular markers of cartilage and bone with special reference to mineralization. We are currently exploring in vitro assays for chemotaxis for mesenchymal cells and endothelial cells.

2. Publications:

Reddi, A.H. and Sullivan, N.E.: Matrix-induced endochondral bone differentiation: Influence of hypophysectomy, growth hormone and thyroid stimulating hormone. *Endocrinology* 107:1291-1299, 1980.

Reddi, A.H., Meyer, J.L., Tew, W.P., Howard, J.E. and Lehninger, A.L.: Influence of phosphocitrate, a potent inhibitor of hydroxyapatite crystal growth on mineralization of cartilage and bone. *Biochem. Biophys. Res. Commun.* 97:154-159, 1980.

Reddi, A.H.: Cell biology and biochemistry of endochondral bone development. Collagen and Related Research 1:209-226, 1981.

Weiss, R.E. and Reddi, A.H.: Appearance of fibronectin during the differentiation of cartilage, bone and bone marrow. J. Cell Biol. 88:630-636, 1981.

Weiss, R.E. and Reddi, A.H.: Role of fibronectin in collagenous matrix-induced mesenchymal cell proliferation and differentiation in vivo. Exp. Cell Res. 133:247-254, 1981.

Rath, N.C. and Reddi, A.H.: Changes in polyamines, RNA synthesis and cell proliferation during matrix-induced cartilage, bone and bone-marrow development. Develop. Biol. 82:211-216, 1981.

Reddi, A.H. and Kuettner, K.: Vascular invasion of cartilage: Correlation of morphology with lysozyme, glycosaminoglycans, protease and protease-inhibitory activity during endochondral bone development. Develop. Biol. 82:217-223, 1981.

Price, P.A., Lothringer, J.W., Baukol, S.A. and Reddi, A.H.: Developmental appearance of the vitamin K-dependent protein of bone during calcification. Analysis of mineralizing tissues in human, calf and rat. J. Biol. Chem. 256:3781-3784, 1981.

Myllyla, R., Tryggvason, K., Kivirikko, K.I. and Reddi, A.H.: Changes in intracellular enzymes of collagen biosynthesis during matrix-induced cartilage and bone development. Biochim. Biophys. Acta 674:238-245, 1981.

Rath, N.C., Hand, A.R. and Reddi, A.H.: Activity and distribution of lysosomal enzymes during collagenous matrix-induced cartilage, bone and bone marrow development. Develop. Biol. 85:89-97, 1981.

Reddi, A.H.: Matrix-induced endochondral bone development: A model for regenerative growth. In Becker, R.O., Thomas, C.C. (Eds.): Mechanisms of Growth Control. (in press).

Reddi, A.H.: Development of Cartilage and Bone. In Jones, C.T. (Ed.): Biochemical Development of the Fetus and Neonate. Oxford University (in press).

Weiss, R.E. and Reddi, A.H.: Fibronectin and Collagenous Matrix-induced Endochondral Bone Formation. In Veis, A. (Ed.): Chemistry and Biology of Mineralized Tissues. Elsevier/North Holland (in press).

Weiss, R.E., Reddi, A.H. and Nimni, M.E.: Somatostatin can locally inhibit proliferation and differentiation of cartilage and bone precursor cells. Calcif. Tiss. Int. (in press).

Reddi, A.H.: Perspectives in the role of extracellular matrix in differentiation and morphogenesis. In Anderson, W.A. (Ed.): Perspectives in Growth and Differentiation. Elsevier/North Holland (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00012-19 LBS
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Infrared and Raman Spectroscopic Studies of Teeth and Bones and Related Synthetic Compounds		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Fowler, B.O. Youmans, P.A. DeGraff, B.A. Lenk, E.V.	Research Chemist Secretary (steno) Purchasing Agent Expert/Consultant	LBS NIDR LBS NIDR LBS NIDR LBS NIDR
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Biological Structure		
SECTION Mineral Chemistry and Structure Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 1.15	PROFESSIONAL: 1.05	OTHER: 0.1
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The main objective is to determine <u>compositional</u> and <u>structural details</u> of the inorganic phase in <u>teeth</u> and <u>bones</u> . <u>Infrared</u> and <u>Raman spectroscopy</u> as well as chemical methods are employed in these studies. Methods are devised for the preparation of synthetic calcium <u>apatites</u> having controlled physical properties (crystal size and perfection) and chemical constituents (e.g., hydroxide, fluoride, chloride, carbonate, water and acid phosphate). The vibrational spectra of these apatites and related compounds are assigned and characterized. Isotopically enriched apatite analogs are prepared to facilitate spectral assignments. The spectroscopic assignments and supplemental spectral data (temperature dependency and polarization) are then utilized to establish compositional and structural details of the apatites in question which include: the type and geometry of constituent ions; the site or number of sites occupied by the ions; orientation of ions; chemical bonding and interactions of ions; and semi-quantitative estimations of the constituents present. The results for these controlled apatite systems are then related to the inorganic phase in calcified tissues.		

Project Description:

Objectives:

The main objectives are to determine compositional and structural details of the inorganic phases in teeth and bones, with special emphasis on normal, abnormal, carious and chemically-treated human tooth enamel.

Methods and Approaches Employed:

Infrared and Raman spectroscopy and chemical methods are the primary tools of these studies. An understanding of the infrared and Raman vibrational spectra of various synthetic apatites and related compounds is necessary to determine corollary compositional and structural details for the inorganic phase(s) of hard tissue. Hence, these studies entail identification of the vibrational origin of infrared and Raman spectral bands for pure hydroxy-, fluor-, and chlorapatite, for mixed apatites containing hydroxide, fluoride, chloride, carbonate, acid phosphate, water and different cations, and for related calcium phosphates. The combined spectral data are then utilized to establish compositional and structural details of these apatites. These include the type of geometry of ions, orientation of ions, chemical bonding and interactions of ions, and semi-quantitative estimations of constituents present. Specialized spectroscopic techniques involving reflectance, polarization, low and high temperature, and high pressure devices are utilized in obtaining spectra. Methods are developed for the synthesis and purification of the compounds studied that require design and construction of specialized apparatus to maintain the rigid experimental conditions (e.g., high temperature and pressure) required to form apatites of controlled chemical and physical properties. Isotopically substituted analogs are prepared to facilitate assignment of spectral bands. The techniques are supplemented by chemical analyses to ascertain purity and chemical composition of the preparations.

Major Findings:

1. Spectroscopic Hydroxide Quantitation and Preparation of Small Crystal Size (~ 1000 Å) Stoichiometric Hydroxyapatite.

Previous Raman quantitation of OH in high-surface area ($\sim 150 \text{ m}^2/\text{g}$) non-stoichiometric apatitic calcium phosphates gave values higher than expected by comparison to chemically derived values. The high deviation of the Raman derived OH values was believed to arise from surface related effects indigenous to small size crystals that have a considerable portion (20% or more) of their total unit cells on their surfaces. Additional spectroscopic data on stoichiometric hydroxyapatites (SHAs), of constant chemistry and structure, progressively smaller in crystal size until approximately one-half of their total crystal unit cells were surface exposed (approximate crystal size in bone) were needed to evaluate the crystal size effect and establish OH reference values for the infrared and, particularly, the Raman method. Three approaches, grinding, thermal maturation and precipitation, were evaluated for preparing small size high-surface area SHA crystals. Crystal size reduction of SHA large crystals was previously found unsatisfactory because of apparent crystal

damage even during gentle grinding as indicated by infrared analyses. The thermal maturation experiments were carried out by (a) precipitating an apatitic solid with Ca/P ratio of 10/6 with a surface area of about $110 \text{ m}^2/\text{g}$, and (b) briefly heating (minutes and longer) this apatite in the temperature range 600 to 900°C in effort to perfect small size nuclei before extensive crystal growth could occur by thermal diffusion from adjacent crystals. The thermal maturation process produced SHAs, but concomitant with acceptable crystal perfection the crystals had grown too large in size to be useful ($\sim 50 \text{ m}^2/\text{g}$) as determined by surface area measurements and electron microscopy. This method has potential for preparing smaller crystal size SHA, but it was not explored in detail. The literature did not reveal methods for preparing SHA with surface areas in excess of about $30 \text{ m}^2/\text{g}$ which corresponded to crystal sizes too large for the studies here. High-surface area small crystal size apatites can be prepared from solution at 25°C ; however, they are usually nonstoichiometric and, even if stoichiometric, considerable uncertainty exists in their degree of phase homogeneity and structural coherence. This uncertainty was reduced, in principle, in the preparations here by (a) using only crystals that were solution matured at 90 to 100°C (maturation at 25°C may take years or never occur), (b) using only preparations that were, from electron micrographs, morphologically discernible as discrete crystalline solids and free of additional phases of poorly-defined variable shape, and (c) complete chemical analyses (Ca , PO_4 , HPO_4 , OH , H_2O and CO_3) and physical characterization. The final preparative method developed involved, overall, initial precipitation at 25°C and pH 12, maturation of the precipitate by boiling at pH 12 for 12 to 72 hours, washing five or more times at 100°C by resuspension to nearly constant pH, collection by centrifugation, drying by lyophilization and then complete analyses. A closed apparatus system was used to minimize uptake of atmospheric CO_2 by the apatites. Glass apparatus was not acceptable because silicate impurities were introduced from the reaction vessel during boiling at the high pH. Polypropylene vessels were found to introduce minimal impurities and were used instead of glass. The initial mixing rates of reactants were varied from hours to minutes in effort to achieve increasing numbers of apatite nuclei prior to boiling and possibly obtain progressively smaller crystal sizes at maturity. After boiling 12 to 72 hours, regardless of differences in initial surface areas (~ 110 to $190 \text{ m}^2/\text{g}$ effected by faster mixing rates), crystal surface areas and sizes did not significantly differ and ranged from about 55 to $65 \text{ m}^2/\text{g}$ for nine different samples. These apatite crystals were needle-like in shape with length, $\sim 1000 \text{ \AA}$ and thickness, $\sim 200 \text{ \AA}$; they were, overall, free of additional phases of poorly-defined shape, and from their physical dimensions, they had about 15 to 20% of their total unit cells on their surfaces. Chemical and physical analyses indicated these apatites were essentially stoichiometric hydroxyapatites of high purity except for minor carbonate impurities ($\sim 0.5 \text{ wt. \%}$). Progressively higher surface area SHAs that approached bone crystal size were desired; however, they could not be prepared using the boiling criterion invoked here; consequently, no further attempts to prepare higher surface area SHAs will be made at this time. Apatites collected at short boiling times, less than two hours, were higher in surface areas, but they were judged unacceptable by electron microscopy because of crystal shape nonuniformities

and uncertainty in their extents of maturation. The SHAs prepared here are appropriate crystal size controls for mature human tooth enamel (except for length) and are suitable for surface and exchange reaction studies and for evaluation of spectroscopic OH quantitation to the size range indicated.

2. Effect of Pyrolytic Atmospheres on Acidic Phosphate Quantitation and Solid-State Compositional Changes in Nonstoichiometric Hydroxyapatites on Aging.

In a collaborative study with Dr. John L. Meyer of compositional defects in nonstoichiometric hydroxyapatites (NSHAs), the HPO_4 contents of these NSHAs plotted considerably lower, as a function of Ca/P ratio, than most values reported in the literature. Consequently, a study was carried out in an effort to explain these differences in HPO_4 contents. The literature HPO_4 values were determined using air pyrolytic methods at 500 to 600°C, whereas vacuum pyrolytic methods at 550°C were used for HPO_4 determinations here. The HPO_4 contents were redetermined on part of these NSHAs that had been stored in a dessicator for about 36 months using vacuum, air and sealed-tube pyrolytic atmospheres at 550°C. The HPO_4 contents obtained under these different pyrolytic atmospheres were not significantly different except for NSHAs that contained considerable carbonate. These pyrolytic results showed that the lower HPO_4 contents were not caused by the different pyrolytic atmospheres, and that secondary reactions, that can cause erroneously high HPO_4 contents, were minimal under the pyrolytic conditions used. However, both the HPO_4 and OH contents of the 36 month old NSHAs had increased substantially as compared to the original analyses at a sample age of about 3 months. Both the increases in HPO_4 and apatite OH in these aged NSHAs that contained about one H_2O per PO_4 suggest that water molecules split to furnish OH for further apatite hydroxylation and/or apatite formation and H^+ for additional HPO_4 formation. These solid-state changes occurred slowly at room temperature. It is very probable that drying at usual temperatures ($\sim 110^\circ\text{C}$) would have accelerated these changes; however, compositional changes with temperature were not explored. Differences in conditions of NSHA preparation, washing, drying temperature, storage environment, surface area, carbonate content, and sample age at analysis time could account for the HPO_4 differences between samples here and those in the literature. In summary, it appears that the HPO_4 values obtained and used here in compositional computations of defects in the NSHAs were not experimentally low, but instead reflected the NSHAs' HPO_4 contents at earlier stages of apatite maturation.

Significance to Dental Research:

Characterization and assignment of the infrared and Raman bands of apatite containing biologically relevant ions and those of related calcium phosphates are essential in establishing corollary structural details for the inorganic phases of teeth and bones. The types and degree of incorporation of hydroxide, fluoride, chloride and carbonate ions, water, acid phosphate and different cations into biological apatites have bearing on the chemical, physical and biological properties of hard tissue.

Proposed Course of Project:

The method developed for preparing small crystal size stoichiometric hydroxyapatites, and also larger size crystals by a previous method, will be prepared for publication after completing further chemical and physical analyses.

The infrared and Raman spectroscopic study for semi-quantitative determinations of hydroxide ions in apatites will be completed using data from the newly synthesized small crystal size apatites and then prepared for publication.

The preparation and characterization of specific biologically relevant synthetic carbonate apatites will be continued. Results will be related, where applicable, to the carbonate components in tooth enamel.

Raman single-crystal symmetry species data on fluorapatite and hexagonal hydroxyapatite and both Raman and infrared powder data on fluorapatite, hexagonal and monoclinic hydroxyapatite, plus additional Raman data to be collected on hydroxide librational modes, will be prepared for publication.

Work will continue on infrared and Raman external mode band assignments for fluoroapatite and both the hexagonal and monoclinic forms of hydroxyapatite and chlorapatite using combined data from band symmetry species, isotopic band shifts, band temperature dependency, band intensity and mixed OH, F, Cl apatites.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00088-08 LBS
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Chemical, Structural, and Morphological Studies on Calcium Phosphates		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Eanes, E.D. Hailer, A.W. Martin, G.N., Jr. Youmans, P.A. DeGraff, B.A. Floyd, S.W.	Research Chemist Chemist Equal Opp. Spec. (Emp1) Secretary (steno) Purchasing Agent Photographer (laboratory)	LBS NIDR LBS NIDR LBS OD LBS NIDR LBS NIDR LBS NIDR
COOPERATING UNITS (if any) Stanford University Synchrotron Radiation Laboratory, Palo Alto CA. Dr. Jonathan L. Costa, NIMH, ADAMHA. Dr. Linda Powers, Bell Laboratories, Murray Hill, N.J.		
LAB/BRANCH Laboratory of Biological Structure		
SECTION Mineral Chemistry & Structure Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 2.48	PROFESSIONAL: 1.0	OTHER: 1.48
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The properties of synthetically prepared <u>calcium phosphates</u> of biological interest are being studied with a variety of ultrastructural and physical-chemical techniques such as electron microscopy, x-ray diffraction, extended x-ray absorption fine structure analysis, B-E-T surface area methods, and standard analytical chemistry procedures. Topics under current investigation include (1) the local structure about Ca^{2+} ions in crystalline and amorphous calcium phosphates (2) the preparation and characterization of synthetic analogues to intracellular mineral deposits such as occur in mitochondria and in subcellular storage organelles, and (3) the formation and properties of precipitates induced in phosphate solutions by the ionophoric translocation of Ca^{2+} across bulk organic solvent barriers.		

1. Project Description:

Objectives:

The purpose of this project is to study the physicochemical and ultrastructural properties of naturally occurring and synthetically prepared calcium phosphate compounds of biological interest. During the year covered by this report, a relatively new technique, Extended X-ray Absorption Fine Structure (EXAFS) analysis, was employed to study some of the structural properties of these compounds. In particular, the technique was used in an attempt to obtain information on how the immediate phosphate neighborhood about the calcium ion differs in amorphous compared to crystalline calcium phosphates.

Another area of interest is in developing in vitro systems to study those properties of calcium phosphates whose expression in vivo are often obscured by overlying cellular and physiological processes. Recent efforts have been directed toward developing appropriate synthetic models of intracellular mineral deposits such as occur in mitochondria and in subcellular storage organelles and of mineral deposits formed by transmembrane transport of Ca^{2+} into PO_4 -rich biofluids such as may occur in matrix vesicles. The principal undertaking in the area of intracellular mineral modeling during the past year was to complete a study on the preparation and characterization of synthetic analogues to the calcium-adenosine phosphate-pyrophosphate complexes that are found in the dense bodies of blood platelets. Particular emphasis was placed on determining the mechanism by which dense bodies can accumulate in vivo large quantities of biogenic monoamine compounds such as serotonin. As part of a new study on membrane controlled precipitation phenomena, an investigation was initiated to establish the types of calcium phosphate phases that can form in phosphate-containing solutions subjected to large inward Ca^{2+} fluxes across an organic solvent barrier. In this study, an ionophoric-mediated, neutral diffusion-exchange technique was used to transport the Ca^{2+} from an aqueous Ca reservoir through the solvent layer for release into the PO_4 solution.

Methods Employed:

A number of calcium phosphate compounds were examined by the EXAFS procedure. These included both stoichiometric and non-stoichiometric hydroxyapatites, carbonate-apatite, octacalcium phosphate, mineral from rat tibial diaphyses, and amorphous calcium phosphate. The Ca K-edge absorption measurements needed to obtain the EXAFS spectra of these compounds were made using the focused x-ray beam line II-3 at the Stanford Synchrotron Radiation Laboratory, Palo Alto, CA. The EXAFS spectra were Fourier transformed to obtain a radial structure function from which was obtained information on the atomic coordination shells about the absorbing Ca atom.

Synthetic dense body analogues were prepared by the spontaneous precipitation method described in last year's annual report. Binding properties were determined by suspending aqueous slurries of freshly prepared analogues in appropriate volumes of either LiCl, KCl, quinacrine, ^3H - or ^{14}C -serotonin solutions. Solids and supernate were separated by either filtration or centrifugation and analyzed chemically, colorimetrically or in a liquid scintillation spectrometer. In some binding experiments, dried solids were mixed with non-aqueous solvents containing the adsorbate, separated and analyzed.

A modified Pressman cell (Pressman, Federation Proc. 32, 1698 (1973)) was used in the Ca^{2+} translocation experiments. In this cell, the Donor (i.e., Ca) and Reaction (i.e., PO_4) compartments were separated by a glass partition. The only communication between the two aqueous compartments was through an organic solvent compartment in common contact with them. The organic solvent used in the present experiments was CHCl_3 . Cationic transport through the CHCl_3 layer was by means of the carrier ionophore, lasalocid acid (X-537A) in concentrations ranging from 2 to 20mM. The Donor compartment contained initially 100mM Na^+ and either 1.33 or 13.3 mM Ca^{2+} . The appearance of these cations in the Reaction compartment was monitored by atomic absorption spectrophotometry of sampled aliquots. The initial phosphate concentration in the Reaction compartment ranged from 0 to 22mM. Sufficient KCl was added to this compartment to bring the initial K^+ concentration to 100mM. In addition, 0.8mM Mg^{2+} and/or 26mM HCO_3^- was added to this compartment in some experiments. Both aqueous compartments were buffered with HEPES. The pH of the Reaction compartment was kept at 7.4, that of the Donor at 7.4 or 7.8. All experiments were done at 25° or 37°C.

Major Findings:

The EXAFS study clarified a number of structural features of amorphous calcium phosphates which heretofore had been points of considerable conjecture. It was found that the mean Ca-O distances in all of the solids examined were essentially the same which indicates that the electrostatic attractions between Ca^{2+} and PO_4^{3-} which bind together these two components in amorphous materials are similar to those in crystalline salts. On the other hand, and in contrast to the crystalline solids studied, the amorphous materials showed sufficient structural disorder that second order atom pair contributions to the EXAFS spectra such as Ca-P and Ca-Ca interactions could not be observed. The absence of these contributions strongly indicate that the amorphous calcium phosphates are truly non-crystalline as their name suggests, rather than microcrystalline in structure. The EXAFS spectrum of rat bone mineral was more similar to carbonate-apatite than to any of the other synthetic apatites studied. This finding is not too surprising as bone mineral contains appreciable carbonate, but it also points up the limitation of EXAFS analysis in establishing the presence of amorphous mineral in bone.

Past studies have shown that Ca-adenosine phosphate-pyrophosphate solids can be prepared synthetically which resemble quite closely in structure, composition, and solubility the membrane bound core material of human blood platelet dense bodies. Such a close resemblance has provided useful insights into certain properties of dense bodies not accessible by more direct means as, for example, the apparently high proton content of the core material. Studies conducted during the past year revealed, however, that the synthetic analogues differed quite markedly from the dense bodies in their ability to bind biogenic amines such as serotonin from aqueous solution. In fact, the level of serotonin binding was similar to that observed with the monovalent cations, Li^+ and K^+ , and approximately 1000 times less than what is needed to account for its in vivo storage in dense bodies. On the other hand, it was found that neutral serotonin can be readily removed from nonpolar organic solvents by the synthetic solids. The additional observation that non-protonable aromatic compounds such as anthracene do not display similar affinities under these nonpolar conditions suggests that a Bronsted-Lowery acid-base reaction is responsible for the enhanced uptake in this

case, i.e., a proton from an acid phosphate group in the solid is transferred to the amine group on the bound serotonin. Thus charged, the serotonin molecule is unable to reenter the non polar solvent. It is postulated that a similar cationization mechanism may account for biogenic amine storage in dense bodies. Only neutral amines can readily traverse the dense body membrane. Once inside, however, the amines become charged and prevented from back diffusion by transfer of protons from the core material. Further, the net retention of these amine compounds in the core can be explained by the fact that the concentration of transferable protons in the solid core material (approximately 1M) far exceeds that found in the cytosol surrounding the dense bodies.

In the ionophore experiments, the principal driving force behind the transport of Ca^{2+} from the donor to the reaction compartment proved to be the counter-movement of K^+ between these compartments. Each movement was coupled to the other by an exchange/diffusion mechanism, i.e., a cycle of ionophore mediated $\text{Ca}^{2+}/\text{K}^+$ exchanges at each aqueous/ CHCl_3 interface and transport via neutral cation-ionophore complexes through the CHCl_3 layer to the opposite interface. Na^+ , Mg^{2+} , and H^+ flows between the aqueous compartments were found to have only minor effects on the Ca^{2+} flow. It was observed that in all experiments, the amount of Ca^{2+} transported into the reaction compartment was sufficient to precipitate calcium phosphate solids. In those experiments where the initial K^+ gradient was several times larger than the initial Ca^{2+} gradient, the solution Ca^{2+} level in the reaction compartment in time actually exceeded by a factor of 4 or more that in the donor compartment. Generally, the first phase to precipitate was amorphous calcium phosphate (ACP). The ACP formed, however, was unstable and in time converted to apatite. Both carbonate and magnesium delayed but did not stop this transformation.

Matrix vesicles, which are small extracellular membranous vesicles located in regions of cartilage and bone undergoing active mineralization, are markedly enriched in Ca^{2+} compared to the cells from which they were derived. This enrichment appears to be accompanied by a loss in intravesicular K^+ (Wuthier, Calc. Tiss. Res. 23, 125 (1977)). However, the means by which Ca^{2+} enters and K^+ leaves these organelles is not known. The results of the present model study suggest that one possible explanation for these cation movements in vesicles is the presence of $\text{Ca}^{2+}/\text{K}^+$ antiporters in their enclosing membrane. It should be noted, however, that such an antiporter mechanism has not been described in any biological membrane system to date although electrogenic $\text{Ca}^{2+}/\text{Na}^+$ antiporters are known to exist in the plasma membrane of nerves and muscles (Racker, Fed. Proc. 39, 2422 (1980)).

Significance to Dental Research:

The deposition of calcium phosphate salts in skeletal tissues is a complex, poorly understood process. Several studies in recent years indicate however, that amorphous calcium phosphate may play an important role in this process, especially as a precursor phase to apatite during the earliest stages of mineral formation. The EXAFS data obtained in this project provide evidence that this ACP is most likely a distinct mineral entity and not a cryptostructural form of some well-known biocrystalline phase such as apatite. One difficulty relating to the presence of ACP in skeletal tissues is that in synthetic precipitation systems this phase cannot be formed de novo at systemic physiological

calcium and phosphate concentrations. The ionophore experiments, however, illustrate one possible means by which skeletal fluid Ca^{2+} levels can be raised locally (e.g. in vesicular spaces) to the point where they exceed the threshold value for ACP precipitation. The reported presence of ACP in matrix vesicles (Schraer and Gay, Calc. Tiss. Res. 23, 185 (1977)) lends evidence to this possibility.

Intracellular calcium precipitation is a promising yet relatively unexplored area of mineralization research. Some evidence has been reported which indicates that the storage and release of calcium and phosphate contained in intramitochondrial granules may be connected in some way with the initial stages of extracellular calcification in bone and cartilage. Although the present studies have been directed toward preparing and characterizing model compounds to platelet dense bodies and in answering questions concerning the role these bodies have in platelet function, the information obtained in these studies should prove invaluable in developing synthetic analogues to intramitochondrial granules.

Proposed Course of Project:

The current EXAFS studies will be continued if possible. Future emphasis will be on surface EXAFS measurements. An example would be the measurement of the EXAFS spectrum of Sr^{2+} adsorbed on the surface of apatite crystals. The intracellular calcification studies will continue with emphasis on preparing and characterizing synthetic models of mitochondrial granules. Future ionophore experiments will explore the effect of other transport mechanisms, such as electrogenic ion movement, on calcium phosphate formation. The use of liposomes in model calcification experiments will also be explored.

2. Publications:

Eanes, E.D.: Crystal growth of mineral phases in skeletal tissues. Prog. Crystal Growth Charact. 3:3-15, 1980.

Termine, J.D., Eanes, E.D. and Conn, K.M.: Phosphoprotein modulation of apatite crystallization. Calcif. Tiss. Int. 31:247-251, 1980.

Eanes, E.D., Costa, J.L., MacKenzie, A. and Warburton, W.K.: Technique for the preparation of solid specimens for x-ray absorption studies. Rev. Sci. Instruments 51:1579-1580, 1980.

Shupe, J.L., Eanes, E.D. and Leone, N.C.: Effect of excessive exposure to sodium fluoride on composition and crystallinity of equine bone tumors. Am. J. Vet. Res. 42:1040-1042, 1981.

Eanes, E.D. and Rattner, S.L.: The effect of magnesium on apatite formation in seeded supersaturated solutions at pH 7.4. J. Dent. Res. (in press).

Eanes, E.D., Powers, L. and Costa, J.L.: Extended x-ray absorption fine structure (EXAFS) studies on calcium in crystalline and amorphous solids of biological interest. Cell Calcium (in press).

Costa, J.L., Eanes, E.D., Fay, D.D. and Hailer, A.W.: Preparation and characterization of synthetic models for the dense bodies of human platelets. Cell Calcium (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00162-05 LBS																		
PERIOD COVERED October 1, 1980 to September 30, 1981																				
TITLE OF PROJECT (80 characters or less) Kinetic and Thermodynamic Characterization of Calcium Phosphate Precipitation																				
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT																				
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Meyer, J.L.</td> <td style="width: 33%;">Research Chemist</td> <td style="width: 33%;">LBS NIDR</td> </tr> <tr> <td>Hailer, A.W.</td> <td>Chemist</td> <td>LBS NIDR</td> </tr> <tr> <td>Lenk, E.V.</td> <td>Expert/Consultant</td> <td>LBS NIDR</td> </tr> <tr> <td>Weatherall, C.C.</td> <td>Biological Aid (biochem)</td> <td>LBS NIDR</td> </tr> <tr> <td>Youmans, P.A.</td> <td>Secretary (steno)</td> <td>LBS NIDR</td> </tr> <tr> <td>DeGraff, B.A.</td> <td>Purchasing Agent</td> <td>LBS NIDR</td> </tr> </table>			Meyer, J.L.	Research Chemist	LBS NIDR	Hailer, A.W.	Chemist	LBS NIDR	Lenk, E.V.	Expert/Consultant	LBS NIDR	Weatherall, C.C.	Biological Aid (biochem)	LBS NIDR	Youmans, P.A.	Secretary (steno)	LBS NIDR	DeGraff, B.A.	Purchasing Agent	LBS NIDR
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Hailer, A.W.	Chemist	LBS NIDR																		
Lenk, E.V.	Expert/Consultant	LBS NIDR																		
Weatherall, C.C.	Biological Aid (biochem)	LBS NIDR																		
Youmans, P.A.	Secretary (steno)	LBS NIDR																		
DeGraff, B.A.	Purchasing Agent	LBS NIDR																		
COOPERATING UNITS (if any)																				
LAB/BRANCH Laboratory of Biological Structure																				
SECTION Mineral Chemistry and Structure Section																				
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205																				
TOTAL MANYEARS: 1.75	PROFESSIONAL: 1.05	OTHER: 0.7																		
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																				
SUMMARY OF WORK (200 words or less - underline keywords) The purpose of this work is to determine the <u>thermodynamic</u> and <u>kinetic</u> factors which regulate the <u>nucleation</u> , <u>crystal growth</u> and <u>maturation</u> of <u>calcium phosphate crystals</u> . This is accomplished by estimating <u>free ionic activities</u> in solution for all species involved in the crystallization process and relating these terms to the observed precipitation steps. A further correlation is then made between the composition of the solution and the properties of the solid calcium phosphate phase in equilibrium with it. The effect of crystallization inhibitors on the precipitation of calcium phosphates is also being studied in order to elucidate their mode of action at crystal surfaces. Emphasis is placed upon inhibitors which occur naturally in physiological systems or which are common therapeutic agents.																				

1. Project Description:

Objectives:

A number of factors appear to regulate the nucleation, crystal growth and maturation of calcium phosphate precipitates under the conditions at which biological calcification occurs. It is the purpose of this investigation to elucidate the kinetic and thermodynamic parameters which control each of the major steps involved in calcification and thereby gain additional insight into the mineralization process itself. Emphasis is placed upon the solution phase and how its composition affects crystallization processes, although the isolated solid phases are also studied with conventional chemical, microscopic and spectroscopic techniques.

Methods Employed:

The calcium phosphate precipitations are performed under conditions of constant temperature and pH. From the analytical concentrations of the reactants, free ionic concentrations and chemical activities of each ionic species are calculated using known thermodynamic equilibrium constants and computed activity coefficients. A computer program has been developed to perform these calculations. Knowledge of the free ionic activities of each species involved in the precipitation provides the necessary kinetic and thermodynamic information for the correlation between events that occur in solution versus those that occur in the solid state. The solid material is isolated from the well-characterized solutions by Millipore filtration and lyophilized. The calcium phosphate precipitates are analyzed for other possible lattice constituents (i.e., acid phosphate, carbonate, and hydroxide) as well as the calcium and phosphate contents.

Major Findings:

The spontaneous precipitation of calcium phosphate is characterized by the formation of an initial phase which is amorphous with respect to x-ray diffraction. This amorphous calcium phosphate (ACP) phase, if left in contact with solution, transforms into a crystalline material with an apatitic-like x-ray diffraction pattern but with the thermodynamic properties of another well-defined calcium phosphate phase, octacalcium phosphate (OCP), $\text{Ca}_8\text{H}_2(\text{PO}_4)_6$. After a reproducible period of time, which is greatly dependent upon solution conditions, this intermediate crystalline phase transforms into a more basic calcium phosphate phase with a tricalcium phosphate (TCP), $\text{Ca}_3(\text{PO}_4)_2$, stoichiometry. This latter phase gradually matures to hydroxyapatite (HA), $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, the thermodynamically stable phase under physiological conditions.

The rate of the amorphous to crystalline transformation has been shown to decrease with increasing pH in the pH range 7-9.25. In contrast, the rate of transformation of the intermediate crystalline calcium phosphate phase to the final apatitic phase is accelerated by an increase in solution pH in this range and becomes immeasurably rapid above pH 9.0. In order to determine whether other mechanisms or precursors might be involved at elevated pH, the calcium phosphate precipitation reaction was investigated throughout the pH range 9.25-12.80. The induction period for the amorphous-crystalline transformation was shown to first

increase with increasing pH and then decrease in the pH range 9.25-12.80. The maximum stability of ACP occurred at a pH of 10.25. At lower pH ACP had a well defined solubility determining molecular unit, but in the pH range 9.25-12.80 a material of variable solubility was formed suggesting a breakdown in the short range order of the amorphous phase. Although nucleation kinetics suggested that an OCP-like phase is a necessary intermediate phase in the amorphous-crystalline transformation which occurs in the pH range 7-9.25, no evidence was found for such a phase at higher pH. In fact, thermodynamic considerations completely ruled out the participation of OCP in the amorphous-crystalline transformation above pH 10.7. It is possible that either a different mechanism for the amorphous-crystalline transformation takes precedence at high pH or that the variable thermodynamic properties of the ACP formed at high pH result in a substrate with varying ability to nucleate the first-formed crystalline form of calcium phosphate.

Significance to Dental Research:

A knowledge of the factors that influence calcium phosphate precipitation is required for a complete understanding of the physiological processes that result in hard tissue mineralization. A thermodynamic approach to the study of calcium phosphate precipitation under simulated in vivo conditions yields basic information that can be related ultimately to conditions that may exist in vital fluids in contact with the mineral phase. The combination of thermodynamic and kinetic methods can provide a better description of those dynamic processes resulting in physiological and pathological calcifications or decalcifications within the body.

Proposed Course of Project:

Future research efforts will further characterize the entire course of the precipitation of calcium phosphate from the initial formation of ACP to its eventual transformation to crystalline HA. Emphasis will be placed on determining how the solution environment affects the kinetics of precipitation processes and the final composition of the inorganic phases. Particular attention will be placed on the role that calcium phosphate crystal growth inhibitors play in influencing the final composition of the mineral phase. Initially, work will center on known physiological and pharmacological inhibitors of calcification and their mechanisms of action at the surfaces of the calcium phosphate precipitates. Since calcification inhibitors are generally proposed as regulators of normal biological mineralization and since they have often been implicated in the initiation and progression of pathological calcification conditions in the body, it would be desirable to extend the fundamental mechanistic studies to a more biologically relevant setting. To this end, the principal investigator will spend the 1981-82 year on a Foreign Work/Study assignment in the laboratory of Dr. Herbert Fleisch at the Pathophysiology Institute of the University of Bern, Switzerland, in order to receive training in new methods to better assess the role and function of physiologically active inhibitors of calcification.

2. Publications:

Reddi, A.H., Meyer, J.L., Tew, W.P., Howard, J.E. and Lehniger, A.L.: Influence of phosphocitrate, a potent inhibitor of hydroxyapatite crystal growth, on mineralization of cartilage and bone. *Biochem. Biophys. Res. Comm.* 97:154-159, 1980.

Meyer, J.L.: Nucleation kinetics in the calcium oxalate-sodium urate monohydrate system. *Invest. Urol.*, (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00028-14 LBS
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Ultrastructure and Cytochemistry of Secretory Cells		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Hand, A.R. Oliver, C. Ho, B. Lenk, E.V. Qwarnstrom, E.E. Doine, A.I. Waters, J.F. Mednieks, M.I. Youmans, P.A. DeGraff, B.A. Floyd, S.W. Frear, C.	Chief, LBS Research Biologist Biologist Expert/Consultant Visiting Fellow Guest Worker Biologist Staff Fellow Secretary (steno) Purchasing Agent Photographer (laboratory) Student Trainee	LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR
Continued on next page.		
COOPERATING UNITS (if any) Dr. Lois Tice, LEP, NIAMDD		
LAB/BRANCH Laboratory of Biological Structure		
SECTION Experimental Morphology Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 6.0	PROFESSIONAL: 3.75	OTHER: 2.25
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords)		
Basic mechanisms of the <u>secretory process</u> are studied in cells of the rat pan- creas, salivary and lacrimal glands. Techniques utilized include light and <u>electron microscopy</u> , <u>cytochemistry</u> , <u>radioautography</u> , and basic biochemical procedures. Major areas of investigation are: (1) the structure and function of the <u>Golgi apparatus</u> and <u>GERL</u> ; (2) experimental pathology and <u>lysosome</u> func- tion in salivary glands; (3) structure and <u>permeability</u> properties of <u>junctional complexes</u> in the rat parotid gland; and (4) the effects of <u>sialographic</u> procedures on the structure of the rat submandibular gland.		

Continuation page: Names, Laboratory and Institute Affiliations.....

Mazariegos, M.R.	Visiting Fellow	LBS NIDR
Wolf, R.O.	Dental Director	LBS NIDR
Omnell, K-A.	Visiting Scientist	CIPC NIDR

1. Project Description:

Objectives:

The basic objective of this project is to obtain further knowledge of the structure and function of secretory cells and their organelle systems. Utilizing electron microscopic, cytochemical, radioautographic and biochemical techniques, cell ultrastructure is correlated with enzyme localization, quantitation of cellular constituents, and glycoprotein synthesis and transport. Our efforts have concentrated on: (1) the structure and function of the Golgi apparatus and GERL; (2) experimental pathology and lysosome function in salivary glands; (3) structure and permeability of junctional complexes in the rat parotid gland; and (4) the effects of sialographic procedures on the structure of the rat submandibular gland.

Methods Employed:

Tissues for morphological examination are fixed by vascular perfusion and prepared by standard techniques. Cytochemical incubations are carried out on 50-75 μ m slices of fixed tissue. Freeze-fracture replicas of resting and isoproterenol stimulated parotid tissue are prepared in collaboration with Dr. Lois Tice, NIAMDD. Biochemical determinations of protein, DNA, amylase, peroxidase, and other enzyme activities follow standard procedures. Rat parotid saliva collected by cannulation of the main excretory ducts is analyzed by polyacrylamide disc gel electrophoresis.

Major Findings:

Structure and Function of the Golgi Apparatus and GERL:

Studies reported last year demonstrated that secretory stimulation of the parotid gland resulted in modulations of the structure and cytochemistry of the Golgi apparatus and GERL. At early times after isoproterenol injection (1-3 hours), GERL was enlarged and strongly reactive for acid phosphatase activity, and immature secretory granules were consistently reactive. At later times (8-12 hours), while acid phosphatase activity in GERL was decreasing, the immature granules were reactive for thiamine pyrophosphatase and appeared to begin formation from the trans Golgi saccule. Additionally, GERL-like structures at the trans face of the Golgi apparatus were reactive for thiamine pyrophosphatase. Exocrine pancreatic acinar cells have now been shown to undergo similar cytochemical changes following stimulation with pilocarpine. Increased acid phosphatase activity is present in GERL and immature secretory granules beginning at 3 hours, and is especially prominent at 7 hours after stimulation. These findings further substantiate the occurrence of physiological modulations of enzyme activity in GERL, and provide additional evidence for its previously described role in secretory granule formation.

Experimental Pathology and Lysosome Function in Salivary Glands:

Previous work has established that the lysosomal system of parotid gland acinar cells is activated in various experimental conditions, such as acute starvation, ethionine administration and liquid diet. Autophagocytosis of damaged acinar cell cytoplasm, and sequestration and degradation of stored

secretory granules are commonly observed. Additionally, macrophages invade the glandular parenchyma and phagocytose acinar cell debris.

The above models deal with the response of a normal gland to injurious stimuli, resulting in reduced function, and, in the case of liquid diet, severe glandular atrophy. We have begun an investigation of the role of the lysosomal system in the recovery of the normal structure and function of hypertrophied glands. Daily injections of isoproterenol for 10 days cause hypertrophy and hyperplasia of the rat parotid gland. The gland wet weight and protein content are increased 3-5 fold, and RNA and DNA content are increased 6-8 times. Secretory proteins (amylase) are also increased, but not to the same degree. Other investigators have shown that the synthesis of proline-rich proteins is markedly increased, that these unusual proteins may make up as much as 50% of the secretory material in isoproterenol-enlarged glands, and that several new proline-rich proteins are found. The individual acinar cells are greatly enlarged and contain abundant rough endoplasmic reticulum and numerous secretory granules which have a less dense content than granules of control parotid acinar cells. When the isoproterenol injections are stopped, the glands return to normal size and structure. We are currently following the recovery of the glands using a combined morphological, cytochemical and biochemical approach. Initial results suggest that the return to normal may take longer than expected, and that secretory protein synthesis and storage, as measured by amylase content, may be poorly regulated in the recovering glands. Future work will entail measurement of lysosomal enzyme levels, and analysis of the morphologic and cytochemical data.

Structure and Permeability Properties of Junctional Complexes in the Rat Parotid Gland:

Previous studies on the fate of exogenous tracers infused retrogradely into the main excretory duct of the parotid gland suggested that the permeability of the junctional complexes between the epithelial cells may be altered following secretagogue stimulation. In an attempt to further define the permeability properties and structural features of the intercellular junctions in the parotid gland, three separate studies have been initiated. The structure of the tight junctions in unstimulated and isoproterenol stimulated tissues is being examined in replicas of freeze-fracture preparations. In unstimulated glands, the tight junctions between acinar cells consisted of a few rows of anastomosing strands or particles on the P fracture face, and corresponding grooves on the E face. At one hour after stimulation, no clearly definable alterations were apparent in the structure of the tight junctions. However, in replicas from tissues 30 minutes after stimulation, initial observations indicate marked changes in the junctional structure; the junctional strands appeared disorganized, and several areas between the lumen and intercellular spaces were free of junctional structures. These results are now being confirmed in glands from animals stimulated 15 and 30 minutes prior to sacrifice.

In order to further characterize the permeability properties of the junctions, a series of retrograde ductal infusions is being conducted. Tissues are examined microscopically to determine the distribution of the tracer, i.e., whether it is restricted to the lumen or has penetrated the junctional complex and permeated the intercellular spaces. Tracers of different molecular size, e.g., cytochrome c (~12,000 daltons), horseradish peroxidase (~40,000 daltons),

lactoperoxidase ($\sim 80,000$ daltons) and catalase ($\sim 240,000$ daltons), are being used to determine if there are size restrictions to the junctional permeability. Different types of stimulation, i.e., β - and α -adrenergic, cholinergic, and peptidergic, will be examined to determine if the changes in permeability are specific to certain types of stimulation. Finally, the infusions will be begun at different times after stimulation in order to establish a time course for the permeability changes. These studies are an important adjunct to the freeze-fracture work, since the degree of "tightness" or "leakiness" of the junctions cannot be stated with certainty based on the structural appearance alone.

Finally, the ability of blood-borne macromolecules to enter the saliva is being studied. Stimulated parotid saliva is collected from the cannulated main excretory ducts of animals injected intravenously with tracers such as horseradish peroxidase. The saliva is electrophoresed and the gels are stained histochemically to detect protein bands indicating the presence of the tracer. Initial experiments have been concerned with establishing the appropriate technical conditions for detecting the tracer in the saliva. Some difficulties have been encountered thus far, possibly due to the small amount of tracer entering the saliva. Larger doses of tracer will be administered to the animals, and if necessary, immunochemical detection methods will be utilized in order to determine if the tracer enters the saliva. The potential significance of the transfer of blood-borne substances into the saliva cannot be underestimated. Pharmacological agents, immunoglobulins, and other serum constituents could thereby gain access to the oral cavity. Thus, the ability to manipulate the permeability of the salivary epithelium may have eventual prophylactic and therapeutic potential.

Effects of Sialographic Procedures on the Structure of the Rat Submandibular Gland:

The effects of retrograde ductal infusion of lipid-soluble contrast medium into the submandibular gland were examined, and compared with our previous study of water-soluble contrast medium. As with the water-soluble medium, the lipid-soluble contrast medium was not retained in the tissue during routine processing for electron microscopy. Attempts to devise an electron dense tracer or alter our processing procedures to retain the contrast medium were unsuccessful. Thus, monitoring the intraglandular pressure during infusion proved critical in assessing the success of the infusion procedure. The appearance of the gland during the earliest stages of infusion, i.e., dilation of the lumina of the intralobular ducts, was similar for both media, suggesting that saliva initially present in the lumina was responsible for these changes. The intercalated ducts showed the most marked alterations of any of the intralobular ducts, while the excretory ducts appeared unaffected. In contrast to the water-soluble medium, the lipid soluble medium did not appear to penetrate the junctional complexes and leak into the intercellular spaces. Thus, the acinar lumina and intercellular canaliculi were markedly dilated, and the acinar cells were severely compressed by the lipid-soluble medium. Discharge of acinar secretory granules both into the lumina and into the lateral intercellular spaces was observed, and at the later stages of infusion, large cytoplasmic "vacuoles" which were in continuity with the lumen were frequently present in the intercalated duct cells. These findings suggest that sialography with lipid-soluble contrast medium may have potentially deleterious effects on the various components of the salivary glands, as well as altering

the appearance of the gland in the radiograph.

Further studies are in progress to characterize the recovery of the glands following the sialographic procedure. Both water-soluble and lipid-soluble media will be utilized.

Significance to Dental Research:

These studies are expected to provide a better understanding of the structure and function of secretory cells. Secretory cells of the major and minor salivary glands provide the fluid environment of the oral cavity, and physiological or pathological changes in their function will greatly affect this environment. Although sialography is used as a clinical diagnostic procedure, little is known of the effects of sialography on the salivary glands. Our studies should broaden the scientific basis of this procedure, potentially increasing its diagnostic utility and decreasing the possible damaging effects on the tissue.

Proposed Course:

The major investigations described above will be continued, as indicated in the narrative for each. Additionally, we hope to initiate studies on secretory and lysosomal enzyme localization by immunocytochemical techniques, peptide and neurotransmitter receptor site localization, and the structure of salivary glands and other tissues in mice with viral-induced diabetes mellitus.

2. Publications:

Hand, A.R. and Ho. B.: Liquid-diet induced alterations of rat parotid acinar cells studied by electron microscopy and enzyme cytochemistry. Arch. Oral Biol. 26:369-380, 1981.

Hand, A.R., and Oliver, C. (Eds.): Basic Mechanisms of Cellular Secretion. Methods in Cell Biology, Vol. 23. Academic Press, Inc. New York. (in press).

Hand, A.R., and Oliver, C.: The Golgi Apparatus: Protein Transport and Packaging in Secretory Cells. In Hand, A.R. and Oliver, C. (Eds.): Basic Mechanisms of Cellular Secretion. Methods in Cell Biology, Vol. 23, Academic Press, Inc., New York (in press).

Qwarnstrom, E.E., and Hand, A.R.: Distribution and effects of water-soluble radiographic contrast medium after retrograde infusion into the rat submandibular gland - a light and electron microscopic study. Arch. Oral Biol. (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00199-05 LBS
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;"><u>In Vitro</u> Studies of Secretory Cell Structure and Function.</p>		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Oliver, C. Hand, A.R. Lenk, E.V. Waters, J.F. Smallwood, V. Youmans, P.A. DeGraff, B.A. Floyd, S.W. Frear, C. Yuasa, Y. Siraganian, R.	Research Biologist Chief, LBS Expert/Consultant Biologist Biologist Secretary (steno) Purchasing Agent Photographer (laboratory) Photographer (trainee) Guest Worker Chief, CI	LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LMI NIDR
COOPERATING UNITS (if any) NCI, POB.		
LAB/BRANCH Laboratory of Biological Structure		
SECTION Experimental Morphology Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 3.46	PROFESSIONAL: 1.52	OTHER: 1.94
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <p> <u>Secretory processes</u> in several cell types are currently under investigation. Cell dissociation and short term <u>culture</u> (up to 1 month) methods have been established for <u>rat exorbital lacrimal</u>, <u>parotid</u> and <u>pancreatic acinar cells</u>. These cultures are being used to study various aspects of the secretory process. Emphasis is being placed on <u>morphological</u>, <u>cytochemical</u> and <u>biochemical</u> characterization of the cultured cells. Uptake and fate of both <u>soluble phase</u> and <u>membrane bound markers</u> by exocrine acinar cells is also being examined <u>in vivo</u> and <u>in vitro</u>. </p>		

1. Project Description:

The primary objectives of this study are to establish procedures for short term culture of isolated exocrine gland acinar cells and to utilize these cultures in investigations of events involved in the secretory process.

Methods Employed:

Isolated exocrine gland acini or individual acinar cells were prepared and maintained as previously described. Membrane reutilization was studied both in vivo and in vitro. For in vivo studies, horseradish peroxidase (HRP) (1 mg/gm body weight) was injected into the saphenous vein of adult, male NIH Swiss mice or Wistar-Furth rats, or native ferritin was instilled retrogradely into the pancreas and parotid gland via the main excretory ducts. Some animals received secretagogue (isoproterenol, 20 mg/kg body weight; pilocarpine, 40 mg/kg body weight) prior to or concomitant with the HRP injection. Animals were sacrificed by vascular perfusion of fixative, at varying times following HRP administration. The glands were excised, and sections incubated for peroxidase activity, or for demonstration of various marker enzymes, i.e., thiamine pyrophosphatase for Golgi saccules and trimetaphosphatase and acid phosphatase for lysosomes. For in vitro studies of membrane reutilization isolated acini were cultured in medium containing 1% HRP (Sigma types VI, VII, and IX), 1% native or cationized ferritin as tracers.

In work reported last year, a previously unrecognized component of the lysosomal system in exocrine acinar cells was described. These basal lysosomes form an anastomosing network adjacent to the basal and lateral cell surfaces. Intravenously administered exogenous tracers are taken up from the lateral and basal cell surfaces in coated vesicles and are initially sequestered in the basal lysosomes. In contrast, lumenally administered tracers are endocytosed from the apical cell surface in smooth surfaced vesicles and accumulate in vesicles and secondary lysosomes near the Golgi apparatus. Administration of secretagogue markedly enhances the uptake of tracer into basal lysosomes. Preliminary in vitro studies using radiolabeled HRP have indicated that there is a significant increase in the amount of tracer internalized by stimulated cells.

The basal lysosomes have been further characterized both functionally and cytochemically. In addition to trimetaphosphatase (TMPase) activity, these lysosomes possess aryl sulfatase, non-specific esterase and cholinesterase activities. The exact nature of the cholinesterase activity has yet to be resolved. These cytochemical localizations are in contrast to that seen in GERL, where in exocrine cells, acid phosphatase is the only enzyme demonstrated to date. These results strengthen the suggestion that the basal lysosomes are distinct from GERL. Functionally, there appears to be a redistribution of TMPase activity following administration of either isoproterenol or pilocarpine in the exorbital lacrimal gland, parotid gland and exocrine pancreas. Following agonist administration TMPase activity is localized in lysosomes adjacent to the Golgi apparatus. The most striking morphological change occurs in pancreatic acinar cells with the basal lysosomes attaining lengths of up to 4-5 μ m following pilocarpine administration. These studies offer additional evidence of a metabolic relationship between receptor activation and lysosomal function.

The uptake of both soluble phase and membrane-bound tracers by isolated resting and carbachol (10^{-4} M) stimulated pancreatic acini in vitro is currently under investigation. Those tracers which bind to the membrane, i.e., cationized ferritin and positively charged horseradish peroxidase, appear to be internalized more avidly than the soluble phase markers, neutral or negatively charged peroxidase and native ferritin. However, once internalized all of the tracers seem to be sequestered in the same compartments, i.e., vesicles, multivesicular bodies, basal lysosomes and secondary lysosomes. To date, none of the tracers have been localized in GERL, Golgi saccules, immature or mature secretory granules. This suggests that internalized membrane is not utilized directly in secretory granule formation. Studies are also in progress to identify antibodies to various membrane components which may then be used to directly follow the internalization and intracellular fate of exocrine acinar cell plasma membrane. Forty monoclonal antibodies to rat mast cell plasma membrane have been screened for cross-reactivity against fixed and frozen sections of rat exorbital lacrimal gland, parotid gland and exocrine pancreas. Of the 40 antibodies screened, 4 were strongly reactive with the cell surface of the acinar cells. Procedures are also being developed for isolation of plasma membrane from exocrine acinar cells to serve as an antigen for the production of monoclonal antibodies specific for the acinar cell surface. The antibodies against the cell surface will be labeled with electron-dense tracers so that their fate within the cells may be followed.

Other studies have concentrated on the secretory apparatus of human blood cells. Electron microscopic cytochemical techniques have been used in the diagnosis of human megakaryoblastic leukemia. These leukemias are difficult to correctly identify by light microscopy. The megakaryoblasts possess a glutaraldehyde sensitive platelet peroxidase (PPO) localized in the cisternae of the rough endoplasmic reticulum and the nuclear envelope, but not in the Golgi saccules. The absence of PPO from the Golgi saccules and its glutaraldehyde sensitivity allow one to differentiate progranulocytes from megakaryoblasts and thus differentiate myelogenous from megakaryocytic leukemias. The human promyelocytic leukemia cell line, HL-60, is purported to be bipotential with respect to its ability to differentiate. Upon exposure to dimethylformamide (DMF), the cells become neutrophilic in appearance, while after exposure to 12-O tetradecanoyl phorbol acetate (TPA), the cells acquire characteristics similar to monocytes. Since neutrophils and monocytes possess quite different mechanisms for formation of secretory granules, it was of interest to examine the HL-60 cells to determine what alterations may be occurring during differentiation. Routine electron microscopic examination suggests that rather than differentiating along 2 separate lines, the HL-60 cells, although originating as a clone, have diverged along the two pathways and that treatment with DMF or TPA may result in the selective killing of one population and promote the differentiation of the other. Enzyme cytochemical studies have shown that after treatment with either DMF or TPA the cells no longer have peroxidase reaction product in the rough endoplasmic reticulum, nuclear envelope, or Golgi saccules, but that the cells do contain peroxidase positive granules. Further studies should help elucidate the mechanism of action of DMF and TPA and characterize the process of differentiation in the HL-60 cells.

Significance To Dental Research:

In vitro studies of exocrine gland acinar cells should provide a greater

understanding of both the controlling mechanisms and synthetic pathways involved in their secretory processes. Salivary gland secretions are absolutely essential for maintenance of the health of the oral cavity. Therefore, knowledge of the normal secretory process is critical to our understanding of many pathological conditions which affect dental health.

Proposed Course of Project:

Cultured exocrine cells will be further characterized with respect to their cellular morphology and cytochemistry, protein synthetic capacity, and response to secretagogues. Additional studies will examine the function of the basal tubular lysosomes, the distribution of membrane receptors, the fate of internalized receptors and ligands, membrane reutilization, and the role of microtubules and microfilaments in the secretory process.

2. Publications:

Greenberg, J.H. and Oliver, C.: Dimethyl sulfoxide reversibly inhibits the pigmentation of cultured neural crest cells. *Arch. Biochem. Biophys.* 204:1-9, 1980.

Oliver, C., Auth, R.E. and Hand, A.R.: Morphological and cytochemical alterations of the Golgi apparatus and GERL in rat parotid acinar cells during ethionine intoxication and recovery. *Am. J. Anat.* 158:275-284, 1980.

Broadwell, R.D. and Oliver, C.: Morphological Basis for the Synthesis and Packaging of Neuronal Peptides. In Barker, J.L. and Smith, T.G. (eds.): The Role of Peptides in Neuronal Function pp. 21-48, Marcel Decker, New York, 1981.

Oliver, C.: Lipofuscin and Ceroid Accumulation in Experimental Animals. In Sohal, R.S. (Ed.): Age Pigments pp. 335-354, Elsevier/North Holland Biomedical Press, 1981.

Oliver, C. and Hand, A.R.: Membrane Retrieval in Exocrine Acinar Cells. In Hand, A.R. and Oliver, C. (Eds.): Basic Mechanisms of Cellular Secretion Academic Press, Inc., New York (in press).

Broadwell, R.D. and Oliver, C.: The Golgi apparatus, GERL and secretory granule formation within neurons of the hypothalamo-neurohypophysial system of control and hyperosmotically stimulated mice. *J. Cell Biol.* (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00217-03 LBS																		
PERIOD COVERED <p style="text-align: center;">October 1, 1980 to September 30, 1981</p>																				
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;"><u>Salivary Systems</u></p>																				
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Wolf, R.O.</td> <td style="width: 33%;">Dental Director</td> <td style="width: 33%;">NIDR LBS</td> </tr> <tr> <td>Hubbard, V.S.</td> <td>Physician</td> <td>NIAMDD PM</td> </tr> <tr> <td>Baum, B.J.</td> <td>Dentist & Biochemist</td> <td>NIA IMA</td> </tr> <tr> <td>Kuhn, G.A.</td> <td>Technician</td> <td>NIDR LBS</td> </tr> <tr> <td>Nivera, B.</td> <td>Technician-COSTEP</td> <td>NIDR LBS</td> </tr> <tr> <td>Papadopoulos, N.</td> <td>Biochemist</td> <td>CC CP</td> </tr> </table>			Wolf, R.O.	Dental Director	NIDR LBS	Hubbard, V.S.	Physician	NIAMDD PM	Baum, B.J.	Dentist & Biochemist	NIA IMA	Kuhn, G.A.	Technician	NIDR LBS	Nivera, B.	Technician-COSTEP	NIDR LBS	Papadopoulos, N.	Biochemist	CC CP
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Papadopoulos, N.	Biochemist	CC CP																		
COOPERATING UNITS (if any) Laboratory of Molecular Aging, NIA Georgetown University School of Dentistry, Washington, D.C. S.D. James, Ph.D. - USN Surface Weapons CTR																				
LAB/BRANCH <p style="text-align: center;">Laboratory of Biological Structure</p>																				
SECTION <p style="text-align: center;">Experimental Morphology Section</p>																				
INSTITUTE AND LOCATION <p style="text-align: center;">NIDR, NIH, Bethesda, Maryland 20205</p>																				
TOTAL MANYEARS: <p style="text-align: center;">1.59</p>	PROFESSIONAL: <p style="text-align: center;">0.9</p>	OTHER: <p style="text-align: center;">0.69</p>																		
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>																				
SUMMARY OF WORK (200 words or less - underline keywords) <p> This project is concerned with mechanisms of production and control of extrinsic (i.e., <u>saliva</u>) and intrinsic (e.g. <u>serum salivary isoamylase</u>) salivary gland products. Human and animal (primarily <u>parotid</u>) <u>saliva</u> chemical constituents and mechanisms are evaluated as related to health, disease and physiological state. Parotid salivary flow rate, protein content and enzymes (particularly lysozyme and amylase) are evaluated in normals and selected disorders. The intrinsic secretion of salivary isoamylase in serum of <u>cystic fibrosis of the pancreas</u> is being studied. Diagnostic application and an understanding of the mechanisms of <u>hyperamylasemia</u> are being sought. </p>																				

1. Project Description

Objectives:

Associating intrinsic and extrinsic salivary secretion and secreted variables with disease, abnormalities and physiological conditions to further the understanding of salivary gland physiology in animals and man is the overall objective of this project.

Methods Employed:

Part of the parotid salivary lysozyme (LZM) is bound and released upon acidification. The lysoplate method, consisting of radial diffusion of LZM in agar containing the substrate M. luteus has been our basic quantitative assay. Purification of salivary lysozyme by agarose column chromatography for a quantitative standard is in progress.

Amylases are being studied as associated with cystic fibrosis of the pancreas. The total amylase is being quantitated by the blue starch method while the serum pancreatic to salivary ratio is obtained by polyacrylamide gel electrophoresis (PAGE) with subsequent amylase activity determined in serial slices of the gel. Utilization of a specific salivary amylase inhibitor from wheat is being investigated as is an iodine development method of our PAGE separated isoamylases in an effort to increase the efficiency and accuracy of obtaining the serum pancreatic to salivary ratio.

Galvanism is being diagnosed in humans with the aid of a battery operated digital millivolt meter measuring the potentials between restorations and the complaint of "metallic taste". Subjects are taste-tested to rule out a sensory mechanism disorder.

Rat parotid salivary peroxidase is separated by PAGE and localized by standard histochemical techniques using hydrogen peroxide and 3,3'-diaminobenzidine-tetra-HCl.

Major Findings:

The mean values of bound (2.36 $\mu\text{g/dl}$) and unbound (3.34 $\mu\text{g/dl}$) parotid salivary LZM, by the lysoplate method, have been established for a population of dental students. Several high values for the total were encountered but generally not repeatable. However, one student, upon several occasions had high values (25x means) without apparent reason (he claims to be a high plaque former).

In anticipation of work with small animals we have perfected a microassay, amenable to automation, for lysozyme with 3-4 orders of magnitude increase in sensitivity over the lysoplate method.

PAGE has been used to evaluate the pancreatic function of patients with cystic fibrosis of the pancreas (CFP) by separating the serum isoamylases into pancreatic and salivary isozymes. Serum pancreatic isoamylase has been shown to be reduced in patients with pancreatic insufficiency. A blood test of this nature would be clinically useful for infants and small children because of the difficulty in obtaining intubated duodenal fluid for pancreatic enzyme testing. A new and second test utilizes tyrosine attached to para-amino-benzoic acid (PABA). Normal pancreatic metabolism splits the PABA from the tyrosine and

PABA is then found in the urine. Significantly less PABA was found in urine of patients with inadequate pancreatic function. The amount of fecal fat, higher in CFP with pancreatic insufficiency, was the third test in the NIAMDD study to determine the appropriateness of the three tests. Preliminary results show concordance between the three tests.

A variety of new dental restorative metals are being employed to circumvent the high cost of dental gold. As a consequence, an increase in adverse reactions may be anticipated. Galvanism, often reported as "metallic taste", has been authenticated in a modest number of patients with bimetallic (usually gold and amalgam) restorations. Electric potentials above 100 mv between such restorations constitutes strong evidence of galvanism; however, there are many persons with bimetallic restorations without "metallic taste" or other evidence of galvanism. We hypothesize that galvanism is a function of the electrolytic quality of saliva. Instrumentation for recording the breakdown potential of saliva has been assembled and a saliva study shown feasible. Saliva will be tested from those persons with diagnosed galvanism and compared with an age and sex matched control population. A second and important aspect of the study is to determine how to avoid the condition and to determine the most efficient treatment for those with galvanism.

Proposed Course:

Institute a study of bound and unbound salivary LZM in conjunction with the blood value and electrophoretically separated saliva protein. Determine the cellular source of salivary LZM by light and electron microscopic immunocytochemical techniques in animals.

Develop an automated microassay for amylase similar to that developed for LZM for small animal experimentation.

Three laboratories will cooperate in a method-comparison study of amylase. The same set of serum samples will be analyzed by different methods for the ascertainment of the pancreatic to salivary ratio. This is to determine a best clinical method to recommend as particularly applicable for CFP study.

Develop monoclonal antibody to human and to rat salivary isoamylases for intracellular molecular tracing. Methods for purification of isoamylase are in progress.

Investigate human salivary peroxidases with respect to variations observed in the rat parotid salivary peroxidases.

2. Publications:

Moutsopoulos, H.M., Karsh, J., Wolf, R.O., Tarpley, T.M., Tylanda, A. and Papadopoulos, N.M.: Lysozyme determination in parotid saliva from patients with Sjögren's syndrome. *Amer. J. Med.* 69:39-42, 1980.

Wolf, R.O. and Weiffenbach, J.M.: Saliva and taste disorders. *Proc. of 28th International Congress of Physiological Sciences, Adv. Physiol. Sci.* 28:341-345, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00283-02 LBS																					
PERIOD COVERED October 1, 1980 to May 31, 1981																							
TITLE OF PROJECT (80 characters or less) The relationship between matrix and mineral in tooth enamel																							
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Yanagisawa, T.</td> <td style="width: 33%;">Visiting Fellow</td> <td style="width: 33%;">LBS NIDR</td> </tr> <tr> <td>Nylen, M.U.</td> <td>Director, IRP</td> <td>IRP NIDR</td> </tr> <tr> <td>Termine, J.D.</td> <td>Research Chemist</td> <td>LBS NIDR</td> </tr> <tr> <td>Lenk, E.V.</td> <td>Expert/Consultant</td> <td>LBS NIDR</td> </tr> <tr> <td>Youmans, P.A.</td> <td>Secretary (steno)</td> <td>LBS NIDR</td> </tr> <tr> <td>DeGraff, B.A.</td> <td>Purchasing Agent</td> <td>LBS NIDR</td> </tr> <tr> <td>Floyd, S.W.</td> <td>Photographer (laboratory)</td> <td>LBS NIDR</td> </tr> </table>			Yanagisawa, T.	Visiting Fellow	LBS NIDR	Nylen, M.U.	Director, IRP	IRP NIDR	Termine, J.D.	Research Chemist	LBS NIDR	Lenk, E.V.	Expert/Consultant	LBS NIDR	Youmans, P.A.	Secretary (steno)	LBS NIDR	DeGraff, B.A.	Purchasing Agent	LBS NIDR	Floyd, S.W.	Photographer (laboratory)	LBS NIDR
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COOPERATING UNITS (if any)																							
LAB/BRANCH Laboratory of Biological Structure																							
SECTION Experimental Morphology Section																							
INSTITUTE AND LOCATION																							
TOTAL MANYEARS: 1.02	PROFESSIONAL: 0.82	OTHER: 0.2																					
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS																							
SUMMARY OF WORK (200 words or less - underline keywords) Previous work has shown that the organic material related to the enamel crystals can be visualized by <u>electron microscopy</u> in thin sections of enamel demineralized by floating on phosphotungstic acid. Whether this enamel material is a preformed structure involved in crystal nucleation and orientation or represents organic material adsorbed to the surface of the crystals is unresolved. The purpose of the present study is to further characterize the structural <u>relationship</u> between <u>enamel matrix</u> material and the <u>enamel crystals</u> , and to obtain basic information on the nature of the organic material.																							

1. Project Description:

In previous work, it has been suggested that the organic structures observed in decalcified sections of dental enamel represent organic coats adsorbed to the surface of the enamel crystals and not preformed macromolecular structures. This suggestion was based in part on random observations which indicated that the shape and dimension of the organic compartments changed in parallel with changes in crystal size during enamel maturation. The purpose of this project is to characterize in a systematic fashion the structural relationship between enamel matrix and enamel crystals, and to obtain basic information on the nature of the organic matrix.

Rat lower incisors were dissected out, freeze-dried or chemically fixed, embedded in plastic, and sectioned on a Gillings-Hamco microtome. Following microradiography, selected areas of enamel were isolated, reembedded, thin-sectioned, and observed in a transmission electron microscope with or without 1% phosphotungstic acid demineralization. Similar procedures were applied to four to six day old hamster molars.

As reported last year, the electron microscopic studies confirmed the existence of an organic envelope, 20-70 Å in thickness, closely apposed to the surface of the enamel crystals. Evidence provided by recent biochemical studies shows that one class of proteins present in dental enamel, the enamelines, is tightly bound to enamel crystals suggesting that the material observed in our sections is the enamelin protein. Since no organic material was observed inside or between compartments, the location of the other major class of enamel proteins, the amelogenins, remains obscure.

In an effort to answer this question, studies were initiated taking advantage of the differential solubility of amelogenins and enamelines in 4M guanidine-HCl. Frozen sections of hamster molars were attached to glass slides and extracted with 4M guanidine-HCl, then fixed, embedded in epoxy resin, thin sectioned, and observed under the electron microscope with or without phosphotungstic acid demineralization. Organic compartment structures were seen surrounding crystals in both control and guanidine treated enamel. The walls of these crystal compartments appeared slightly thinner and sharper in guanidine-treated than in control samples, a difference especially marked in the most immature enamel. Also, the spaces between crystallites were less electron dense in treated than in control samples. Together, these findings suggest that in immature enamel, material with the solubility properties of amelogenins makes up only a small part of the wall material in addition to being diffusely distributed between the growing crystals. The majority of the wall material, however, appears to be enamelines, judging from its resistance to prolonged guanidine extraction.

In addition, new studies were begun to examine in greater detail the relationship between apatite and enamel proteins, using synthetic apatite and protein-free bovine enamel crystals reacted in vitro with amelogenins and/or enamelines previously isolated from bovine enamel. Preliminary observations indicate that the bovine amelogenins and enamelines were strongly bound to the protein-free bovine enamel crystals. Also both classes of enamel proteins were bound to synthetic apatite. They showed compartment structures similar

to native enamel crystallites in situ after treatment with phosphotungstic acid. However, amino acid assay data showed a slight difference in composition between the original enamel proteins and the proteins bound to the crystal surface.

Future Course:

The principal investigator has returned to Japan following the completion of his fellowship program. He plans to pursue and complete the studies described above.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00285-02 LBS
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Regulation of Protein Secretion in Salivary Glands		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Mednieks, M.I. Hand, A.R. Wolf, R.O. Hyunh, K-C. Ho, B. Youmans, P.A. DeGraff, B.A. Cumberbatch, K.	Staff Fellow Chief, LBS Dental Director Student-trainee Biologist Secretary (steno) Purchasing Agent Student-trainee	LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR
COOPERATING UNITS (if any) De Wys, W., Div. Canc. Treatment, Clin. Inv. Branch, NCI; Jungmann, R.A., Northwestern University; Dowd, F., Creighton University.		
LAB/BRANCH Laboratory of Biological Structure		
SECTION Experimental Morphology Section		
INSTITUTE AND LOCATION NIH, NIDR, Bethesda, Maryland 20205		
TOTAL MANYEARS: 1.54	PROFESSIONAL: 1.05	OTHER: 0.49
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Molecular <u>mechanisms of action</u> are studied in <u>parotid gland acinar cells</u> to determine regulatory events associated with <u>protein exocytosis</u> . In addition to standard biochemical, immunological and morphological methods recently developed experimental techniques such as <u>photoaffinity labelling</u> (8-azido cyclic [³² P]-AMP), <u>enzyme linked immunosorbent antibody technique (ELISA)</u> and <u>microscopic examination of subcellular fractions</u> are part of the experimental design. Cellular responses to <u>receptor interactions</u> of parotid cells with <u>β-agonists</u> have been studied using measurements of <u>cyclic AMP-dependent protein kinase</u> as an index. The majority of the enzyme activity (>60% of the total) is extra-nuclear and the remainder is in the nucleus. In response to stimulation with isoproterenol cyclic AMP-dependent protein kinase activity is increased in the cytoplasmic particulate fraction which consists largely of granules. Redistribution of <u>protein kinase isozymes</u> occurs after stimulation (type I appears in the cytosol whereas only type II is present in controls).		

1. Project Description:

Scope and Background:

Involvement of cyclic AMP in the release of enzymes from salivary gland secretory cells is firmly established and has been directly linked to receptor interactions of β -adrenergic agonists. While morphologic changes resulting from hormonal stimulation have been extensively documented, little information is available describing the molecular mechanisms involved in these reactions. The aim of this study is to examine the changes in cellular compartments associated with secretory processes resulting from stimulation with catecholamines and to identify regulatory events occurring at these sites. The experimental focus is to investigate intracellular distribution of cyclic AMP-dependent protein phosphorylation reactions in rat parotid glands resulting from in vivo and in vitro stimulation of protein exocytosis by isoproterenol.

Specific Objectives:

1. To devise a means of rapid and reliable subcellular fractionation of rat parotid cells into biochemically defined and morphologically identifiable components.
2. To employ measures of cyclic AMP-dependent protein kinase activity as an index of intracellular events which are stimulus responses to cell surface receptor interactions using isoproterenol as the effector.
3. To correlate such signal processing on a cellular and biochemical level to sequential events in degranulation and protein exocytosis by immunocytochemical means.

Methods:

The Experimental System:

Rat parotid glands, stimulated either in vivo or in vitro with isoproterenol, as well as parotid saliva after stimulation, are employed in this study. This model system is useful in that together with biochemically measurable stimulus responses (in the tissue and in saliva), a series of morphologic changes associated with degranulation can be followed employing light and electron microscopy.

Biochemical Procedures:

Standard laboratory procedures are employed, for example, enzyme assays (protein kinase, acid phosphatase, α -amylase, etc.), chromatography (ion-exchange and gel filtration), electrophoresis and cell fractionation procedures. Additionally a modification of an affinity labelling technique using an analog of cyclic AMP, 8-azido cyclic AMP (8-N₃-cAMP), is employed. The technique allows virtually exclusive radiolabelling of the protein kinase regulatory subunits and subsequent covalent bonding to the receptor protein by a photolysis reaction. This eliminates the problem of exchange and nonspecificity encountered in older methods.

Morphological Methods:

Light and electron microscopy are used routinely to follow morphologic changes due to isoproterenol stimulation of parotid tissues. Additionally, various cell fractions are pelleted, fixed, sectioned and evaluated for organelle content and integrity.

Immunological Methods:

Antibodies to soluble proteins are prepared by injecting rabbits with purified antigen preparations. Immunization with a commercial acid phosphatase (Porcine, Sigma) resulted in rabbit sera with a titer of 32-64 (\log_2) as measured by Ouchterlony double diffusion techniques. The antiserum was tested for specificity employing fluorescein isothiocyanate (FITC) labelled double antibody binding methods on frozen sections of rat parotid and prostatic tissue. A more sensitive assay was developed for antibody to acid phosphatase using an enzyme linked immunosorbent assay (ELISA).

Project Status:

Events associated with the synthesis, transport, packaging and export of secretory proteins are under homeostatic control and respond to extracellular signals as well. Control of gene functions is fundamentally affected by protein modifying enzymes and it is likely that cyclic AMP-dependent protein kinase plays such a role in regulating protein exocytosis in parotid acinar cells.

To date, using cyclic AMP-dependent phosphorylation as an index for intracellular regulatory events, we have established the following:

1. The majority of cyclic AMP-dependent protein kinase activity in parotid acinar cells is either contained in organelles or is associated with membranes of specific cell structures.
 - a. The nuclear protein kinase activity constitutes 20-30% of the total and is almost exclusively associated with chromatin.
 - b. In the extranuclear fraction >60% of the total activity is associated with granule membranes and <30% is cytosolic/soluble.
 - c. Time and dose dependent in vitro stimulation results in increased specific activity in the cytosolic particulate fractions, but has no effect on the nuclear fraction at the optimal dose during early stimulation times.
2. Using ion exchange chromatography, a redistribution of cyclic AMP-dependent protein kinase isozymes has been established.
 - a. The type I isozyme appeared in the extranuclear fraction after cell stimulation.
 - b. An increase was found in the R_I/R_{II} subunit ratio on membranes of a purified granule fraction.
3. The distribution of two other marker enzymes (one lysosomal, the other granule) has been followed as a function of in vitro stimulation of parotid tissue with isoproterenol.

- a. Acid phosphatase, associated with a particulate extranuclear fraction, appears to decrease after stimulation and increase in the soluble fraction as determined both colorimetrically and immunochemically.
- b. α -amylase subunits, electrophoretically demonstrated as whole granule components, can be found to increase in the incubation medium as determined both by electrophoretic and colorimetric methods.

From these findings it can be concluded that cyclic AMP-dependent protein kinase is present both in the nuclear and cytoplasmic fractions of parotid acinar cells at highly segregated/compartmental sites. Additionally, our data show that both the enzyme activity as well as its components undergo a redistribution after cell stimulation. A feasible hypothesis for a mechanism in regulating hormonally activated protein exocytosis may be as follows: A direct relationship exists between receptor interaction with β -agonists, activation of adenylate cyclase and increases in intracellular cyclic AMP. Furthermore, activation and redistribution of the effector entity, cyclic AMP-dependent protein kinase, occurs at segregated subcellular sites. Our results implicate phosphorylative modification of proteins to occur in both the nuclear and cytoplasmic fractions of the cell. We suggest: (1) that regulation or implementation of the secretion of stored (in granules) protein occurs in the cytoplasm; (2) that regulation of transcriptional events, i.e., synthesis, transport and packaging, is initiated in the nucleus and is, at least in part, controlled by the action of cyclic AMP-dependent protein kinase.

Work in Progress:

Three related studies are currently being undertaken:

1. The completion of the study, reported above, of protein kinase isozyme distribution in in vitro stimulated parotid tissue. For this purpose an affinity labelling (with photoactivated 8-N₃-cAMP) procedure is employed. Additionally, redistribution of other functional (enzyme) proteins is monitored using immunologic probes (ELISA assays and FITC-labelling techniques).
2. A comparison study is underway of chronically in vivo stimulated parotid glands to ascertain whether the proliferative/hypertrophic responses of this treatment are reflected in the distribution of cyclic AMP-dependent protein kinase regulatory subunits. This approach also lends itself to the investigation of progressive effects of (hyper) stimulation on changes in transcription-related events. For example, mRNA production and new protein synthesis and transport through intracellular compartments (RER→Golgi→GERL→granules) can be followed employing immunochemical and immunocytochemical methods.
3. A third study has been initiated whereby a comparison is made between secretory proteins in saliva, collected from the cannulated duct, to protein extracted from the tissue (granule component) itself.

Planned Studies:

Critical experiments for elucidating mechanistic aspects in the regulation of (exocrine gland) protein secretion are the characterization and identification of covalently modified, endogenous phosphate acceptor proteins.

New methodology has currently become available which is directly applicable to addressing this problem:

- a) the use of specific antibodies produced by a mouse spleen cell system, immortalized by hybridization to a myeloma tumor cell line.
- b) the use of a synthetic phosphate donor analog ($[\gamma]$ thio-ATP) in the isolation (by Hg affinity column chromatography) of a parotid acinar cell substrate protein(s).

Relevance to Dental Research:

Elucidation of mechanisms of action of salivary gland secretory events on a cellular and molecular level can be useful in understanding hormonally regulated exocrine processes in general. Specific applications to dental research might be found in the area of pharmacologic manipulation. For example, salivary gland products might reflect altered exocrine function of some diseases such as cystic fibrosis and drug treatment effects may be evaluated by assaying excretory gland products. Cyclic nucleotides and their analogs have been employed experimentally in treating several neoplastic disorders where the defect is related to hormonally controlled receptor reactions. It is therefore conceivable that use of these compounds may be applied to disorders of secretion.

2. Publications:

Mednieks, M.I. and Jungmann, R.A.: Selective expression of type I and type II cyclic AMP-dependent protein kinases in subcellular fractions of concanavalin A-stimulated rat thymocytes. Arch. Biochem. Biophys. (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00315-01 LBS
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) The Role of Glutathione in Secretory Cells		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Whitson, S.W. Hand, A.R. Reddi, A.H. Youmans, P.A. DeGraff, B.A. Floyd, S.W.	Guest Worker Chief, LBS Research Biochemist Secretary (steno) Purchasing Agent Photographer (laboratory)	LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR LBS NIDR
COOPERATING UNITS (if any) Southern Illinois University		
LAB/BRANCH Laboratory of Biological Structure		
SECTION Experimental Morphology		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 1.15	PROFESSIONAL: 1.0	OTHER: 0.15
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less, underline keywords) The purpose of this research is to characterize the relationship of reduced <u>glutathione</u> (and associated enzymes) to <u>secretion</u> , particularly its possible importance to the function of the <u>Golgi</u> apparatus, its role in disulfide bond formation of secretory proteins and its function in cell recovery (including membrane recycling). The two models being employed to investigate glutathione in secretory processes are the <u>isoproterenol</u> -stimulated <u>acinar</u> cells of the rat <u>parotid</u> gland and <u>cartilage</u> and <u>bone</u> cells of demineralized matrix-induced endochondral bone. Enzyme assays of <u>glutathione peroxidase</u> , which utilizes reduced glutathione as a substrate, and <u>glutathione reductase</u> , which generates reduced glutathione from the oxidized form are being performed. Preliminary data suggest that in isoproterenol stimulated parotid glands there is a peak of glutathione peroxidase activity 4 hours post-injection and glutathione reductase levels rise significantly between 1 and 4 hours post injection. In the <u>bone-induction</u> system, glutathione peroxidase peaks on day 3 after implantation of demineralized bone matrix and then remains elevated during cartilage and bone development. Glutathione reductase also peaks on day 3 but falls during both cartilage and bone formation.		

1. Project Description:

Background:

It is well established that reduced glutathione and NADPH are required as substrates for glutathione peroxidase and glutathione reductase in red blood cell membranes to prevent autooxidation and maintain red blood cell shape and function. In addition these two enzymes have been found in large amounts in liver where they are associated with detoxification reactions.

Certain genetic disorders which affect red blood cell function have been traced to these enzymes or to glucose-6-phosphate dehydrogenase which is a key enzyme in cellular reduction of NADP^+ to NADPH.

More recently it has been found that this same enzyme/substrate complex is responsible for preventing autooxidation in neutrophils and macrophages during the metabolic burst accompanying phagocytic activity. In these cells, the reduced glutathione/oxidized glutathione ratio falls from 5-10:1 toward 1:1. The ability of this enzyme system to return the cytoplasm to a normal ratio rapidly is a requirement for continued cell function and survival. In this vein, a recent study found that isolated spleen macrophages and lymphocytes could be maintained in cell culture only when there were adequate levels of reduced glutathione in the fetal calf serum.

Reduced glutathione has been used successfully as a preventive treatment for aflatoxin-B1 induced carcinoma of the liver. It prevents an increase in liver size and maintains the organ architecture and cell ultrastructure near normal. As a result of this study, it has been suggested that reduced glutathione may have a functional role in the maturation and/or maintenance of the Golgi apparatus. In diethylnitrosamine induced carcinoma of the liver, there are increases in both reduced glutathione and γ -glutamyltranspeptidase activity in precancerous cells. Such cells are reportedly less susceptible to other subsequently injected cytotoxins, perhaps due to the increase in cellular reduced glutathione. The precise mechanism of action of reduced glutathione in chemically induced carcinoma awaits further clarification.

With regard to secretion, glutathione has received little attention. It is recognized that reduced/oxidized glutathione ratios are critical for microtubular assembly which is required for the secretory event itself, and for protein synthesis. In addition, in those secretory proteins containing disulfide bonds (e.g., procollagen, link protein in cartilage, osteonectin, fibronectin, type III and type IV collagens) a two-step enzymatic model has been proposed in which cysteamine oxidase and reduced glutathione act in tandem to form these bonds. Finally, inasmuch as glutathione peroxidase has been shown to be important in lipid oxidation, one could speculate that this enzyme might increase in activity just subsequent to induced glandular secretion as the cell membrane is being recycled, or elevated in secreting connective tissue cells where secretory vesicles are formed by the Golgi apparatus and fuse with the plasmalemma within 15-30 minutes.

Objective:

The objective of this project is to determine the extent to which reduced glutathione is involved in secretion. The initial experiments are designed to answer three major questions:

- 1) Do the activities of glutathione peroxidase and glutathione reductase rise during or just subsequent to secretion in induced glandular secretion, and are they elevated during the active secretory phases of cartilage and bone production?
- 2) Do reduced glutathione/oxidized glutathione ratios change during a secretory burst and if so, what is the time frame?
- 3) If reduced glutathione levels rise intracellularly during or subsequent to secretion, are those levels sufficiently elevated to detect histochemically?

Preliminary Results:

Preliminary data suggest that in isoproterenol stimulated parotid glands, there is a peak of glutathione peroxidase activity 4 hours post-injection and glutathione reductase levels rise significantly between 1 and 4 hours post-injection. In the bone-induction system, glutathione peroxidase peaks on day 3 after implantation of demineralized bone matrix and then remains elevated during cartilage and bone development. Glutathione reductase also peaks on day 3 but falls to near control values during both cartilage and bone cell formation.

Significance:

Salivary glands and bone, two tissues essential for the maintenance of oral health, are examples of cellular systems specialized for the production of secretory materials. Understanding better the role of glutathione in these tissues is important because it should provide valuable new information on the entire secretory process, including the development and maintenance of the Golgi apparatus during cell maturation in both health and disease. When the recent in vivo evidence that glutathione may be produced in the liver and transported through the blood stream to be utilized by other cells in the body is coupled with the possibility that the red blood cell is responsible for reducing much of the oxidized NADP^+ to NADPH, the importance of the vascular supply to secretory cells becomes more critical. For instance, bone cell formation apparently requires a vascular bed as a precursor event. It is well documented that increased oxygen tension is required for bone cell maturation. Perhaps reduced glutathione and NADPH blood levels are equally important factors.

Proposed Course:

The principal investigator intends to finish the work on the three primary objectives listed before returning to SIU. There, further development of enzyme assays and histochemical procedures to fully characterize the role of glutathione will be continued.

Annual Report of the Laboratory of Developmental Biology & Anomalies
National Institute of Dental Research

The major efforts in the Laboratory of Developmental Biology and Anomalies are on the prevention and treatment of inherited and acquired defects in oral-facial development, the possible role of environmental agents and of genetic factors in oral-facial malformations, connective tissue formation and degradation, and the interaction of normal as well as tumor cells with matrix proteins.

The number of laboratory personnel has been relatively stable. John Hassell joined this Laboratory from the National Eye Institute. He has studied various teratogens as well as glycoconjugates in developing tissue. He will work closely with the individuals in the Craniofacial Development Section.

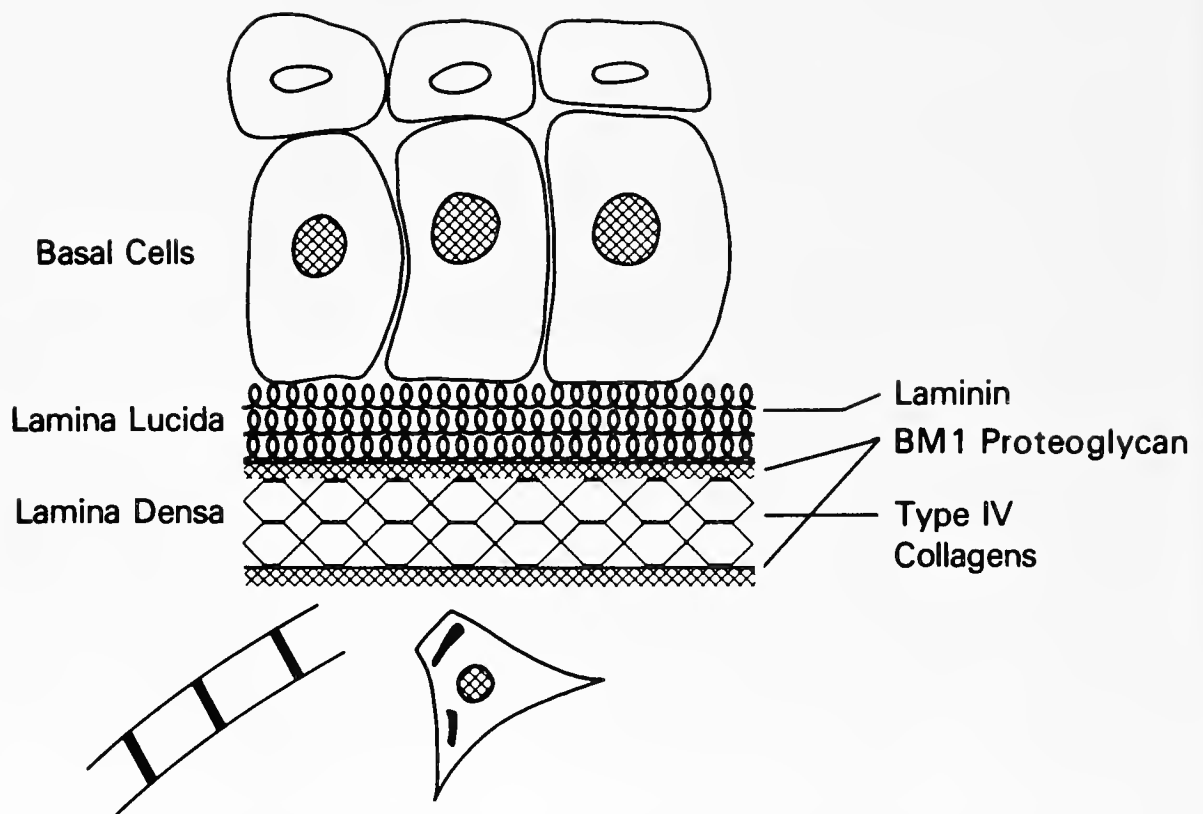
Connective Tissue Section

Basement Membrane - Structure, Function and Alterations in Disease - Basement membranes are thin extracellular matrices that separate epithelial cells from underlying stroma. They appear to be of particular importance in defining tissue structure during development and during tissue repair. Basement membranes contain collagen, glycoproteins, and proteoglycan. Considerable progress has been made in determining the structure and components of basement membrane. Common to all basement membranes are type IV collagen, the major structural element; laminin, a glycoprotein which binds the epithelial cells to the basement membrane; and a heparan sulfate proteoglycan which controls the permeability of the basement membrane. The distribution of these components within the various zones of basement membrane is shown in Figure 1.

Several individuals in the Laboratory are studying the involvement of basement membranes in disease processes. The composition of basement membrane synthesized by normal and diabetic animals has been compared. These studies indicate that the levels of heparan sulfate proteoglycan are markedly reduced in diabetes. Since this proteoglycan regulates the passage of proteins through the basement membrane, decreased levels could explain the increased porosity of diabetic basement membranes. Further, it is proposed that the thickening of basement membranes in diabetes could be a compensatory hypertrophy induced by the change in permeability caused by the loss of the heparan sulfate proteoglycan.

Tumor cells are often less adherent than normal and their attachment to collagen was studied. Nonmetastatic tumor cells attach best to type I collagen and use fibronectin as an attachment factor. In contrast, the cells from metastatic tumors bind preferentially to type IV collagen and use laminin as an attachment factor. Injection of metastatic tumors cells treated with antibody to laminin markedly decreases the number of lung metastases in mice. These studies indicate the importance of laminin in the penetration of metastatic tumor cells into tissue spaces.

A number of immunological diseases involve basement membranes. Recently, we have investigated Chagas' disease, a fibrotic disorder occurring in individuals infected with T. cruzi. Previous studies established that these individuals have circulating antibody which reacts with connective tissues.



We observed that this antibody reacted with basement membrane and was entirely directed against laminin. These antibodies appear to develop against a laminin-like protein on the surface of the parasite and subsequently react with laminin in the host's basement membranes. Similar observations have been made on sera from patients with African sleeping sickness but not with other parasitic or acquired diseases.

It is well known that patients with bullous pemphigoid, a blistering disorder of skin and mucosa, have antibody which reacts with epidermal but not other basement membranes. We have used this antibody to define the component with which it reacts in the epidermal basement membrane. Human epidermal cells in culture have been found to produce the antigen which is a large protein containing disulfide linked chains of 200,000 daltons. This protein is unique to epidermal basement membrane and does not resemble any of the other known components of basement membranes. While its function is not known, it is closely associated with the cell surface.

Molecular Biology of Collagen - We have recently established a group working on the regulation of expression of connective tissue genes. In developing systems, qualitative and quantitative changes in the proteins synthesized are determined by the transcription of DNA. We have recently found that chondrocytes treated with BUdR synthesize less type II collagen, cartilage proteoglycan and chondronectin, but increase their synthesis of type I collagen. The mechanism by which these genes are selected for expression and are coordinately controlled is not yet known, but is being investigated.

Biology of Cell-Matrix Interactions - The chondrocyte-specific attachment protein, chondronectin, has now been isolated in pure form from human as well as from chicken serum. The protein is distinct from other attachment factors. Binding of chondronectin to cartilage matrix involves the interaction of chondronectin with proteoglycan as well as with collagen. Antibodies have been prepared to chondronectin and used in determining its tissue distribution and levels in various types of sera.

Smooth muscle cells have been found to attach preferentially to type V collagen by means of an intrinsic membrane protein. Type V collagen is normally found in close association with the cell surface of smooth muscle cells and this interaction may represent the normal mechanism of attachment of these cells to their matrix.

In collaboration with scientists in the Laboratory of Biological Structure, NIDR, we have tested the biological activity and examined the tissue distribution of a newly discovered protein from bone, osteonectin. Osteonectin binds to both collagen and to mineral and therefore may link the matrix and inorganic components of mineralized tissues. In situ, it is masked by the mineral phase. The protein isolated from humans is being used to produce antibodies which will be used in the clinical study of conditions such as osteogenesis imperfecta and osteoporosis.

The "link" protein of cartilage which stabilizes the interaction of the cartilage proteoglycan with hyaluronic acid has been found in other tissues including the sclera and blood vessels. Link protein has a strong affinity

for type I collagen, and its presence in noncartilage tissue suggests that it has functions in the body in addition to its previously characterized role in cartilage. This possibility is under study.

Chemotaxis and Wound Healing - We have extended our studies on the chemotaxis of phagocytic cells to a variety of other cell types. These studies show that a growth factor from platelets, the platelet derived growth factor (PDGF) is chemotactic for smooth muscle cells and fibroblasts. Protein and RNA, but not DNA synthesis are required for chemotaxis. Other growth factors are not active as chemoattractants. Since PDGF is released in wounds following the aggregation of platelets, it may play a dual role as a wound hormone. First it could attract cells into the wound and then stimulate their proliferation.

Tumors have a variety of means to ensure their survival in the host. They produce substances that attract capillaries, the angiogenic factors. We have found that various tumors produce factors, possibly the angiogenic factors, that are chemotactic for endothelial cells.

Tumors have been found to produce a substance that blocks the chemotaxis of phagocytic cells. This factor may help the tumor cells in avoiding elimination by the immune system. This factor could also account for the loss of ability of tumor-bearing individuals to fight infection.

Genetic and Environmental Factors in Birth Defects - Mice homozygous for the gene FLD are born with multiple fractures. Studies indicate that the type and the amount of collagen in the affected bone are normal. Morphological studies have shown that the mineralization of bone and not cartilage is impaired and our data indicate that the defect resides in the ability of the bone to mineralize. This mutant should be useful in testing nutritional factors that may improve bone mineralization.

Jervine, a poisonous plant alkaloid, was found to be teratogenic in mice. C57 and A strain mice produce young with malformed limbs when treated with Jervine. Offspring of CRN mice treated with Jervine develop neural tube defects. Some strains of mice such as the Swiss Webster are resistant to the drug. These studies demonstrate that differences in genetic backgrounds of the mice are important in determining their response to the drug.

Craniofacial Development Section

Neural Crest - Neural crest cells migrate to a variety of sites in vivo and differentiate into several phenotypes including melanocytes, nerves, myoblasts, chondrocytes, fibroblasts, etc. We have found that the neural crest cells will attach to collagen in the presence of fibronectin and that fibronectin is a chemoattractant for them. It is possible that such factors guide the neural crest cells in vivo.

A factor (PPF) in serum that causes neural crest cells to differentiate into melanocytes has been isolated from serum. The factor is a protein of about 50,000 daltons. It also enhances the differentiation of melanoma cells. Antibody has been prepared to PPF and will be used to determine the tissue producing it and its cellular distribution.

Teratogen Assays - Previously we reported that cultures of differentiating limb bud and neural crest cells could be used as a rapid and simple system for screening drugs for teratogenic activity. Now we have simplified these tests so that all phases can be carried through in microwells. Using the limb bud cell system, we have tested a number of suspected and proven teratogens for activity. A good correlation was found with in vivo tests. In some studies, serum from animals treated with compounds such as hexachlorophene, were tested in our assay. Serum from these animals was strongly teratogenic. These systems allow rapid screening of drugs and their metabolites for possible detrimental effects on developing organisms. Biological substances, such as cell attachment factors and extracellular matrix components are also added to these systems to directly determine their role in growth and differentiation.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00006-21 DB
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Studies on chemotaxis in animal cells		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Schiffmann, E. Seppa, H.E.J. Seppa, S. Gleiber, W. Vasanthakumar, G. Somerman, M.	Research Chemist Visiting Associate Visiting Fellow Postdoctoral Fellow Visiting Fellow Staff Fellow	DB NIDR DB NIDR DB NIDR DB NIDR DB NIDR DB NIDR
COOPERATING UNITS (if any) NCI, NIH: NIMH, NIH		
LAB/BRANCH Laboratory of Developmental Biology & Anomalies		
SECTION Connective Tissue Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland		
TOTAL MANYEARS: 6.05	PROFESSIONAL: 5.15	OTHER: .90
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SUMMARY OF WORK (200 words or less - underline keywords) We are attempting to understand molecular events in animal cell <u>chemotaxis</u> . We have studied migratory behavior in both <u>phagocytic cells</u> and a number of other differentiated cells that synthesize and remodel biological matrices. A partially purified <u>tumor-derived antileukotactic</u> factor may exert its effect by decreasing <u>cell adherence</u> and the formation of <u>toxic O₂ species</u> . The active material may be an ester. Processing the chemotactic signal in leukocytes may involve the inactivation (by phosphorylation) of a protein which inhibits <u>phospholipase A₂</u> , an enzyme required for chemotaxis. Studies on leukocyte <u>adherence</u> , a principal requirement for chemotaxis, show that these cells may use <u>laminin</u> as an attachment factor. <u>Fibroblasts</u> are attracted to certain growth factors and materials from fibrotic tumors. <u>Endothelial cells</u> respond to materials from tumors that also contain <u>angiogenic</u> activity. These findings are relevant to mechanisms of tumor survival. <u>Bone cells</u> are attracted to materials from demineralized bone, powder, suggesting a role for chemotaxis in bone induction.		

INTRODUCTION

Chemotactic behavior appears to be involved in a number of normal and pathological processes. Phagocytes, the major inflammatory cells, arrive at sites of bacterial infection by responding to attractants released by bacteria. Phagocytes then destroy the pathogens and debride the wound. Fibroblasts, responding to other chemical signals, enter the affected area at a later time to effect repair. Neural crest cells are attracted by growth factors, a phenomenon which may be important in stages of growth and development. Both fibroblasts and endothelial cells apparently migrate in response to substances emitted by tumors. The former cell contributes to the fibrotic capsule surrounding certain tumors, perhaps enabling the malignant cells to be protected from the host's immune system. The latter cell may also aid in the survival of the tumor by taking part in an angiogenic response. Our studies include the in vitro chemotactic response of phagocytes and other animal cells. With the aid of defined attractants such as formylated peptides we can probe molecular events of chemotaxis in phagocytes. We are focusing on the regulation of motility in these cells in our studies on the characterization of an anti-chemotactic material from tumors. Tumors may utilize such materials in escaping detection of the immune surveillance system of the host. In other cells such as fibroblasts and endothelial cells we are studying the motile response induced by growth factors and tumor-derived substances.

Methods - Neutrophils and macrophages were used as phagocytic cells. These were each obtained from animal peritoneal exudates: neutrophils from rabbits, and macrophages from guinea pigs. Chemotaxis assays were carried out in Boyden chambers. Anti-chemotactic material was extracted from mouse fibrosarcomas and purified by gel filtration, ion exchange and high performance liquid chromatography. Other animal cells were grown in tissue culture to maintain stocks. Chemotaxis in these cells (fibroblasts and endothelial cells) was assayed in Boyden chambers, with the use of filters that in some cases were precoated with collagenous substrates.

Results

A. Phagocyte chemotaxis. This has been studied from a number of aspects. In examining the modulation of migration we have focused upon the characterization of a low molecular weight (~ 400 daltons) anti-chemotactic material, probably a peptide, from highly malignant tumors. The production of such substances may enable the tumor cell to escape detection by the immune surveillance system of the host, contributing to survival of the tumor. Improved isolation procedures include a one step gel filtration, followed by ion exchange and high performance liquid chromatography. Studies on functional groups of the material indicated that esterification with diazomethane enhances activity while acetylation reagents had no effect. Perhaps a carboxylic ester may be required for activity. In another attempt to characterize the tumor factor we incubated tumor cells with ¹⁴C tyrosine. This amino acid was incorporated into an active fraction isolated by gel filtration. This finding is consistent with earlier indications from amino acid analysis that active material contained tyrosine. Studies on the

mechanism of action of the tumor factor indicated that adherence of both neutrophils and macrophages was inhibited. Since a principal requirement of the chemotactic response is adherence, this action of the factor would obviously interfere with migration. Another study indicated that active oxygen (O_2) production was stimulated by the tumor factor. These products may contribute to immobilizing the cell by disrupting its membrane organization. These findings may give insight into the ability of the tumor to subvert the phagocytic defense of the host.

In studies on processing the chemical signal in chemotaxis, it was found previously that inhibitors of methylation block chemotaxis and phospholipid methylation. However, the release of arachidonic acid from methylated phospholipids also appears to be necessary for motility. In collaboration with D. Bareis and F. Hirata (NIMH) it has now been shown that methylation inhibitors block this release when it is stimulated by chemoattractants (formylated peptides), but not by ionophores. The significance of this is that receptor-mediated turnover of methylated phospholipids may play a role in processing the chemical signal, perhaps as a second messenger. The release of arachidonic acid is also inhibited by the presence of the protein lipomodulin, (itself an inhibitor of chemotaxis) whose synthesis is induced by glucocorticoids. It has now been found in collaboration with F. Hirata, NIMH, that chemoattractants stimulate the phosphorylation of this protein, inactivating it. This phosphorylation reaction may be an important step in initiating the release of arachidonic acid, which in turn is converted to metabolites that may be essential for cell motility.

In collaboration with V.P. Terranova (NIDR) and L. Liotta (NCI) studies were initiated on the nature of adherence in neutrophils. Highly metastatic tumor cells, like neutrophils, must penetrate basement membrane of endothelial cells in blood vessel walls on their way to their targets. The tumor cells use laminin as an attachment protein to type IV collagen. Both these proteins are constituents of basement membrane. We determined whether neutrophils used an attachment mechanism similar to that of tumor cells. Neutrophils were found to attach to substrates including type IV collagen preferentially through laminin, while fibronectin had no effect. Laminin, but not fibronectin, stimulated cell motility. Antibody to laminin, but not to fibronectin, inhibited both attachment and chemotaxis. A similar effect was observed on the penetration of neutrophils into human amnion, a physiological matrix. The amnion system was developed (L. Liotta, NCI) to assay penetration of highly motile cells (tumor and PMN) through physiological barriers. Finally, the presence of laminin in neutrophils was demonstrated by immunofluorescence in intact cells and electrophoresis of immunoprecipitates from neutrophil extracts. These findings suggest that highly motile cells may use similar mechanisms in emigrating from capillaries to their extravascular targets.

B. Connective tissue-type cells

Fibroblasts. These cells, active in wound repair, were shown previously to migrate in gradients of fibronectin and its cell-binding fragment. Now it has been found that platelet-derived growth factor (PDGF), a polypeptide growth factor released by aggregating platelets, is a true attractant for fibroblasts and smooth muscle cells. Other growth factors (insulin, EGF, FGF, NGF) are not active. Chemotactic responsiveness appears to depend upon protein and RNA synthesis but not upon DNA synthesis. Both motile behavior and mitogenic activity are stimulated by similar concentrations of PDGF, suggesting that the same receptor is involved. However, stimulation of chemotaxis can also occur at lower levels of PDGF than those necessary to produce an equivalent mitogenic response. These results suggest that PDGF, as a "wound hormone", may have two roles in wound repair: attraction of fibroblasts into the affected area, and stimulation of subsequent proliferation of these cells.

We are also investigating a possible mechanism for the formation of a connective tissue capsule around certain tumors. Since fibroblasts appear in increased numbers in wounds, they may be responding to injury at the tumor site. The tumor may be producing materials that both attract fibroblasts to the site and stimulate their proliferation. The cells in the capsule may produce substances required by the tumor as well as providing protection to the tumor from the host's immune system. In studies on the mechanism of capsule formation, we have as a first step determined whether conditioned media from human tumor cell lines contained chemoattractants for fibroblasts. It has now been found that four human breast carcinoma cultured cell lines produce potent attractants for human and mouse fibroblasts when the tumor cells are cultured in a defined medium (without serum) with added growth factors (i.e., insulin, transferrin, estradiol, and thyroxine). Partial characterization of the most active conditioned media indicates that the attractant has a molecular weight from 10,000 to 100,000 daltons and is a protein (inactivated by heating above 80° and by treatment with trypsin). Results of anion exchange chromatography suggest that the material may be heterogeneous. These studies may enlarge our understanding of the mechanisms which tumors use to ensure their survival in the host.

Endothelial cells. The formation of a vascular supply is an important step in development, inflammatory processes, wound repair, and tumor growth. These angiogenic processes could be initiated by a chemotactic response of endothelial cells. We have, therefore, studied chemotaxis in these cells to materials from sources such as tumor cells likely to contain angiogenic factors. Conditioned media from transformed fibroblasts, but not from normal cells, contained chemotactic activity. HB₄ cells, derived from transformed murine 3T3 cells induce vasoformative sarcomas. However, these cells do not behave like endothelial cells since they produce in culture a potent attractant for bona fide endothelial cells. It is likely, then, that the vasoformative activity of HB₄ cells depends upon their attracting endothelial cells from the host. The attractant appears to be a protein (30-50 kilodaltons) and is angiogenic. The tumor cells themselves do not respond well

to their own conditioned medium, but are attracted to PDGF, suggesting that they behave more like fibroblasts than like endothelial cells. These studies suggest that chemotaxis may play a major role in angiogenesis; may also add to our understanding of the mechanisms for survival (induction of angiogenesis) of tumors; may be useful in the rapid detection of angiogenic substances; and could be helpful in distinguishing between cell types on the basis of their chemotactic response pattern.

Bone cells. In collaboration with H. Reddi, LBS, we have initiated a project on the possible role of chemotaxis in the induction of bone formation. It has been shown previously (H. Reddi) that demineralized bone powder subcutaneously implanted in mice induces new bone formation at the site of implantation. A well defined progression in the arrival of cell types (leukocytes, fibroblasts) occurs at the site prior to the appearance of the actual bone forming cells, the osteoblasts. It was possible that these cells were accumulating in response to chemoattractants released at the site. We, therefore, tested whether demineralized bone powder as well as matrix components that might be involved in bone remodeling stimulated migration of osteoblasts. Since attachment is necessary for cell migration, we also studied this function. Fibronectin promoted the attachment of both mouse and rat calvaria cells to type I collagen. Attachment was inhibited by blocking protein synthesis. This was not fully overcome by fibronectin, suggesting a requirement for another protein. Fibronectin also attracted both types of cells. In addition, the mouse cells migrated toward PDGF and a crude factor from demineralized matrix. Partial purification of this material with ammonium sulfate precipitation has yielded active material in the 50 to 70% fraction. Laminin (50-100 $\mu\text{g/ml}$) stimulated directed migration of rat cells. These results suggested that specific attachment factors and attractants may play a role in bone formation. These may include growth factors and well characterized connective tissue components that have already been shown to promote a variety of developmental events. In the case of bone formation they may appear at different stages of the process and contribute to determining their sequence. It is possible that these studies may give insight into formation and remodeling of other hard tissues such as teeth.

Proposed course of the project.

Focus will be on the identification of the tumor-derived anti-leukotactic factor. We plan to accumulate sufficient material for definitive mass spectrum analysis and amino acid determination. We will continue functional group studies to characterize the material. We want to determine whether the tumor material has other immunosuppressive activities, such as an inhibition of lymphocyte activation and antibody-dependent cytotoxicity.

The characterization of the tumor-derived attractant for fibroblasts will be pursued. Ammonium sulphate fractionation will be carried out prior to ion exchange chromatography. The effect of the purified protein upon collagen synthesis and secretion of lysosomal enzymes will be studied. We will attempt to generate an antibody from the purified attractant, which in turn may permit identification of fibrotic tumors. The response to this protein of other cells (phagocytes, smooth muscle, and endothelial cells) will be tested. In addition the subcellular distribution of the attractant will be studied to determine whether it is a membrane or intracellular component.

The osteoblast-directed chemotactic activity of demineralized bone will be purified. The effect of this attractant upon synthesis of macromolecules (such as connective tissue components) by responding cells will be studied, and the influence of growth factors and hormones (parathormone, prostaglandins, vitamin D metabolites) upon chemotaxis will be examined. In addition, the requirements, if any, of the synthesis of macromolecules for chemotaxis will be assessed. In collaboration with J. Termine (LBS) we will determine whether his newly described "osteonection", a bone specific glycoprotein of 32,000 M.W. is chemotactic for bone cells.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00009-20 DB
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Chemistry and biosynthesis of connective tissue		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Martin, G.R. Rohrbach, D. Stanley, J. Szarfman, A. Terranova, V.P. Vigny, M. Woodley, D. Yaar, M. Prats, I. Star, V. Wagner, C. York, V.	Ch, Lab. Dev. Bio. & Anomalies Postdoctoral Fellow Guest Worker Visiting Associate Research Associate Visiting Fellow Expert Visiting Fellow Biologist Biological Aid Biologist Biological Aid	DB NIDR DB NIDR DB NIDR DB NIDR DB NIDR DB NIDR DB NIDR DB NIDR DB NIDR DB NIDR DB NIDR
COOPERATING UNITS (if any) Johns Hopkins University; NEI, NIH: NCI, NIH: University of Minnesota and Max-Planck-Institute for Biochemie		
LAB/BRANCH Laboratory of Developmental Biology & Anomalies		
SECTION Connective Tissue Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland		
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SUMMARY OF WORK (200 words or less - underline keywords)		
<p>The purpose of this project is to study the <u>formation</u>, function and <u>destruction</u> of connective tissue components in normal and diseased states. Particular attention is directed toward <u>collagen</u> and <u>proteoglycan</u>. Current aspects of this project include (1) characterization of the matrix components in a tumor which produces basement membrane, (2) the role of collagen in <u>diseases</u> and (3) interaction of tumor cells with collagens.</p>		

Role of attachment factors in binding cells to basement membrane

Previously we showed that laminin, a large basement membrane glycoprotein, serves as a specific attachment protein binding epithelial and endothelial cells to basement membrane collagen. These studies have now been extended to certain phagocytic cells and to tumor cells. These studies show that polymorphonuclear leucocytes have laminin on their surface and use it to bind to basement membrane collagen. In vivo it is likely that as one step in the passage of these cells from capillaries they use laminin for attachment to the basement membrane.

Terranova, Schiffmann, Vasanthakumar, Yorke, Liotta

Transformed cells have been shown to be less adherent to substrate than normal cells. Here we have compared the attachment of metastasizing and nonmetastasizing tumor cells from mice with normal mouse cells. The normal and nonmetastasizing tumor cells attach better to type I than type IV collagen and use fibronectin in their attachment. The cells in cultures of metastatic cells were found to be heterogeneous. The cells that attached rapidly to laminin substrates were found to produce more metastases when injected into mice than the cells from the original cultures. The cells that did not attach readily to laminin produced only a few metastases. Further, it was shown that antibody to laminin with the metastatic cells markedly decreased the number of metastases. These studies indicate that the ability of transformed cells to bind to laminin is necessary for these cells to move to secondary sites. It is possible that methods will be found to block the binding of these cells to laminin.

Terranova, Martin, Liotta, Yorke, Prats

Alterations in Basement Membranes in Diabetes

It is well known that certain basement membranes including nerve, capillary and glomerular become grossly thickened in diabetes. This thickening of basement membranes is thought to interfere with the exchange of materials between cells and blood. The cause of the thickened basement membrane is not known but could involve either increased synthesis or decreased degradation. We have examined the synthesis and levels of various basement membrane macromolecules in the EHS tumor grown in normal and diabetic mice. Three models of diabetes are under study. These include genetically diabetic mice (db/db) with high serum glucose and insulin levels, and mice treated with streptozotycin or virus to destroy the β -cells in their pancreas. The animals with destroyed β -cell function have high serum glucose and low serum insulin. The results of our studies show that normal levels of laminin and type IV collagen are present in the tumors grown in diabetic animals. However, the levels of a basement membrane specific proteoglycan are reduced. This proteoglycan is a heparan sulfate proteoglycan and was originally isolated in LDBA (see Hassell *et al.*, PNAS 77: 4494, 1980). It is believed that the function of this proteoglycan in the basement membrane is to act as a permeability barrier preventing the passage of proteins across the basement

membrane. The reduced proteoglycan levels would explain the increased porosity of the basement membranes in diabetes. Further the change in permeability of the basement membrane could include a compensatory synthesis of basement membrane to restore function and in this way, generate the thickened basement membrane.

Rohrbach, Hassell, Martin, Kleinman, Wagner, Star

Antibodies to Basement Membrane in Chagas' Disease and African Trypanosomiasis

It is well known that some patients infected with *T. cruzi* and *T. rhodesiense* developed a variety of degenerative changes in their tissues long after the parasites have been eliminated. Further, it has been observed that such patients have circulating antibodies that react with a variety of normal connective tissues. We have been studying the histological sites reacting with the Chagas' antibody. Our studies indicate that the Chagas' antibody reacts with basement membranes. Various connective tissue proteins were examined for their ability to react with the Chagas' antibody and a strong reaction was observed with laminin, but not types I-V collagen, fibronectin, heparan sulfate proteoglycan or other proteins. Similar observations were made with serum from patients with African sleeping sickness but not other diseases such as malaria, leishmaniasis, Schistosomiasis, heart disease or cancer. The ability to induce antibody to laminin appears to be rather specific for these trypanosomal diseases. It appears that these parasites have a laminin like protein that induces an immunological reaction with the production of antibody reacting with host protein. The antilaminin antibody may have a role in inducing the degenerative changes in these diseases and be of use in monitoring the occurrence and progression of these reactions.

Szarfman, Terranova, Martin

Nature of the Bullous Pemphigoid Antigen

Patients with Bullous Pemphigoid are subject to severe blisters due to separation or weakening of the forces binding the dermis to the epidermis. It had been noted previously that antibody and complement are deposited along the epidermal-dermal basement membrane and that these patients have circulating antibody reacting with the epidermal basement membrane. This antibody has been used to identify the antigen in the basement membrane. The antibody was not found to react with fibronectin, type IV collagen, laminin or BM1 proteoglycan. Mouse and human epidermal cells in culture were found to react with the antibody, while fibroblasts and cells from the EHS tumor did not. Epidermal cells were labeled with radioactive amino acids and extracted with neutral salt solutions. The antisera precipitated a disulfide linked protein with chains of 200,000 daltons. The antibody from the serum of 10 different patients precipitated the same protein, while serum from other diseases including pemphigus did not. These studies indicate that there is a protein unique to squamous epithelium such as lip, skin and esophagus to which antibody is produced in the blistering diseases.

Stanley, Yaar, Beckwith, Woodley

Binding of Acetylcholinesterase to Basement Membrane

Acetylcholinesterase, the enzyme degrading acetylcholine, is localized in the neuromuscular junction in the basement membrane that separates the nerve ending from muscle. Acetylcholinesterase exists in several different molecular forms. The largest form is assymmetric and the form located in the neuromuscular junction. It contains a collagenous segment. These studies were designed to determine the molecular basis of the binding of acetylcholinesterase to the basement membrane. Immunofluorescence studies with antilaminin antibodies and anti BM-1 proteoglycan antibodies showed that laminin and BM-1 proteoglycan as well as acetylcholinesterase are concentrated in the neuromuscular junction. The enzyme was found to bind strongly to BM-1 proteoglycan and laminin but not to type IV collagen or fibronectin. Interestingly when the collagenous portion of the enzyme was removed by collagenase, its ability to bind to the basement membrane components was destroyed. Further antibodies to type V collagen precipitated the intact enzyme but not after removal of the collagenous portion of the enzyme. These studies may explain why acetylcholinesterase is localized to the neuromuscular basement membrane.

Vigny, Grotendorst, Martin

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00024-15 DB												
PERIOD COVERED October 1, 1980 - September 30, 1981														
TITLE OF PROJECT (80 characters or less) Developmental processes in genetically controlled malformations														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Brown, K.S.</td> <td style="width: 33%;">Medical Director</td> <td style="width: 33%;">DB NIDR</td> </tr> <tr> <td>Harne, L.C.</td> <td>Bio Lab Technician (Animal)</td> <td>DB NIDR</td> </tr> <tr> <td>Strong, D.M.</td> <td>Bio Lab Tech (Animal)</td> <td>DB NIDR</td> </tr> <tr> <td>Omnell, M.L.</td> <td>Visiting Scientist</td> <td>IR NIDR</td> </tr> </table>			Brown, K.S.	Medical Director	DB NIDR	Harne, L.C.	Bio Lab Technician (Animal)	DB NIDR	Strong, D.M.	Bio Lab Tech (Animal)	DB NIDR	Omnell, M.L.	Visiting Scientist	IR NIDR
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COOPERATING UNITS (if any) Howard University; St. Agnes Hospital, Baltimore; Univ. Washington, Seattle; NCI, NIH; NEI, NIH; NIAMDD, NIH; and NIEHS, NIH														
LAB/BRANCH Laboratory of Developmental Biology & Anomalies														
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SUMMARY OF WORK (200 words or less - underline keywords) The objectives of this project are to describe the <u>genetic mechanisms</u> and <u>developmental processes</u> in <u>mutant and highly inbred animals</u> with hereditary predisposition to <u>congenital malformations</u> , particularly involving the face and limbs, and to utilize these animals as experimental systems for the study of the processes of congenital malformation. <u>Mouse strains</u> with hereditary malformations as Mendelian or non-Mendelian traits have been discovered in this laboratory or are obtained from others. Comparison of normal and abnormal development are carried out in <u>embryos of timed gestational age</u> using gross examination of living embryos, whole mount preparations and histological sections as well as biochemical analyses of tissues and of cultured organs and cells. <u>Genetic analysis</u> involves segregation analysis, selection of sublines, cross breeding of abnormal and normal lines and genetic linkage studies. Agents such as <u>drugs</u> , <u>vitamins</u> and <u>hormones</u> are used as probes both for the study of gene action in hereditary malformations and for the study of possible human teratogens.														

The use of mutation produced defects of development continues to be the major approach of our research. Mutations are studied that result in malformations as well as those that sensitize the mouse to the teratogenic effects of various drugs.

Cartilage and Bone Mutants.

Three independent mutant genes that result in dwarfism have been studied in detail. Two of these, cartilage matrix deficiency (cmd) and brachymorphic (bm) have defects in the synthesis of cartilage proteoglycan. Little or no synthesis of the core protein occurs in cmd mice and their cartilage lacks this macromolecule. The bm/bm mouse has reduced sulfation of the chondroitin sulfate side chains of the proteoglycan and reduced cartilage matrix. The Dmm gene reduces the production of type II collagen in cartilage producing a very fragile matrix. The affected Dmm/Dmm and cmd/cmd animals are very similar in appearance and both have cleft palate, short snout with protruding tongue and disproportionately severe shortening of the limbs and they die at birth. At the tissue level both have severe dysfunction of the growth plate of the growing endochondral bone with reduced bone growth. The bm/bm mice live and are fertile with variation in size depending on other genes in their background.

The Dmm and cmd genes result in quantitative specific defects in the production of major molecular species of the cartilage matrix. Thus they are candidates for several types of study of the genetic control and biochemical interaction of molecules in the formation of cartilage matrix. We are starting to examine the RNA of the Dmm/Dmm mouse to see if a change in the message can be observed. Since the interaction between the various macromolecules of cartilage is not understood these mutants can be used to explore these interactions. Preliminary crossbreeding experiments have not resulted in evidence of additive effects between the two genes but the numbers are not sufficient to detect an increase of 1/16 in the dead which would be expected if (Dmm/Dmm, cmd/cmd) resulted in early death.

Mutant mice with fragile bone due to a severe defect in the mineralization of osteoid, the fore leg defect (fld/fld) mouse, are being studied. This recessive trait is associated with normal cartilage formation and mineralization but a severe delay and abnormal pattern of mineralization of osteoid. The bones of the newborn are unusually soft, and frequently bent or broken. About one of ten affected newborn lives to weaning. The affected adult has broader than normal long bones with deformity of the pelvis and a "bulldog" like bow-legged posture. Serum, calcium, phosphorus, and alkaline phosphatase are normal, as is the phosphatase of cultured fibroblasts. The type and amount of collagen synthesized by calvaria and long bone are normal as are the incorporation of sulfate and glucosamine. A spotty deposition of mineral is observed along the mineralization front. The collagen fibers of the bone appear smaller and less electron dense than normal although the banding pattern is normal. Further studies of this mutant are in progress to assess vitamin D and parathyroid status. The fld/fld mouse may be a model for certain forms of osteogenesis imperfecta in the severe recessive

category (type IV) in man. It is possible that the mutant could be used to assess factors increasing bone formation.

Craniofacial Defects.

We have studied a mutant mouse (Er) born without an oral cavity. Morphological studies have shown that the epithelial surfaces in the oral cavity and airway as well as on the external surface of the body are fused. We have discovered that the basis for this lethal anomaly is a defect in the production of Filaggrin in the epithelium. Filaggrin is a 26.5K histidine rich protein involved in the keratinization of the epithelium. When keratinization is impaired, opposing endothelial surfaces adhere and fuse.

The cellular mechanism for the failure of closure of the cranial neural tube in the cranioschisis (crn/crn) mouse has been found to be a transient defect in the cytoskeleton of the paraneural mesenchyme present at the time of neural tube closure. The cells of the mesenchyme adjacent to the neural tube lose their intracellular and cell-substrate contacts and form rounded blebs. This abnormality of mesenchyme lasts less than twenty-four hours and varies in severity and location but causes a failure of cranial neural tube closure. The spinal neural tube is normal. The stock of animals with this defect (CRN) is unusually sensitive to the effects of cytochalasin, an inhibitor of microfilament formation presumably because the genetic defect and cytochalasin impair similar processes.

It has been possible to induce these and other defects in mice with Jervine, a plant alkaloid known to induce craniofacial defects in grazing animals. It has been found that various strains of mice differ greatly in their response to Jervine. Swiss Webster mice appear to be resistant while A/J and C57BL/6J are susceptible. The pattern of defects produced in A/J and C57BL/6J (primarily shortened limbs and facial bones) differs from those in CRN (neural tube defects). Swiss Webster and CRN mice are resistant to the skeletal defects but do have neural tube defects, although only at very high doses in Swiss Webster.

Future Plans.

Study of the biochemical control of the collagen and proteoglycan synthesis in the cmd and Dmm mutants and in cultured chondrocytes from each mutant together and in isolation are planned in combination with several investigators. These may indicate the nature of the control of cartilage matrix synthesis both at the message level and any feedback between collagen and proteoglycan biosynthesis. Study of the timing of the appearance of the specific macromolecules in development using antibodies will identify the biochemical changes associated with cartilage formation. The studies of the defective calcification process in fld/fld will attempt to specifically identify the defective process both in vivo, in cultured cells and in the teeth of the mutants.

Various tissues of the craniofacial region differ in the expression of the Er/Er phenotype. The developmental timing of filaggrin synthesis in the oral epithelium and skin of mutants will be compared with normals using specific antibodies. These findings will be correlated with the studies of the biosynthesis of Filaggrin to examine the role of keratinization of surfaces in maintaining the integrity of intraoral surfaces and skin structures. The metabolism of vitamin A in the OEL Er and normal mice will be further studied using labeled retinoids to specify the pathogenesis of the teratogenicity of the vitamin in OEL and its possible role in modifying the Er phenotype.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00025-15 DB												
PERIOD COVERED October 1, 1980 - September 30, 1981														
TITLE OF PROJECT (80 characters or less) Regulation of connective tissue gene expression during development														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Sobel, M.</td> <td style="width: 33%;">Research Associate</td> <td style="width: 33%;">DB NIDR</td> </tr> <tr> <td>Kaul, R.</td> <td>Visiting Fellow</td> <td>DB NIDR</td> </tr> <tr> <td>Vuust, J.</td> <td>Visiting Scientist</td> <td>DB NIDR</td> </tr> <tr> <td>Young, M.</td> <td>Postdoctoral Fellow</td> <td>DB NIDR</td> </tr> </table>			Sobel, M.	Research Associate	DB NIDR	Kaul, R.	Visiting Fellow	DB NIDR	Vuust, J.	Visiting Scientist	DB NIDR	Young, M.	Postdoctoral Fellow	DB NIDR
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SUMMARY OF WORK (200 words or less - underline keywords) The purpose of this project is to understand the molecular mechanism by which <u>genes</u> for <u>connective tissue</u> proteins are <u>differentially regulated</u> during normal development and in disease states. We are using <u>recombinant DNA technology</u> and conventional methods in nucleic acid biochemistry and cell culture to study the structure and expression of genes coding for both (1) extracellular and cell associated structural proteins, e.g. <u>collagen types I-V</u> and <u>proteoglycan</u> and (2) attachment proteins e.g. <u>fibronectin</u> , <u>chondronectin</u> , and <u>laminin</u> .														

The collagens are a family of proteins with common structural properties which constitute the principal protein component of the extracellular matrix in animal tissues. It is likely that the synthesis of each of the collagen types which are found in different tissues of higher vertebrates responds to a tissue-specific, developmentally regulated differentiation program. In addition, other connective tissue proteins such as attachment proteins (e.g. fibronectin, chondronectin, laminin) and proteoglycans are tissue-specific and appear to be coregulated with the several collagen types.

We are studying several systems in which collagen synthesis is modulated. In chick embryo fibroblasts, we are studying the regulation of type I collagen gene expression as well as the expression of the fibronectin gene. In chick chondrocytes, we are characterizing the mechanism by which type II collagen, chondronectin, and cartilage-specific proteoglycan gene expression can be manipulated in vitro, resulting in an expressed phenotype similar to that of fibroblasts. In mouse epithelial cells, we are studying the control of type IV collagen and laminin gene expression. Our approach to study the control of these genes and to understand the molecular mechanism by which they are regulated during normal and pathologic development, is to use recombinant DNA plasmids which contain sequences complementary to the DNA of these genes. With these specific probes we can (a) measure the levels of particular mRNA species in different cell populations and (b) examine the genomic structure of such cells. We have already constructed and identified recombinant DNA plasmids for several of the genes for connective tissue proteins and are currently using them in the hybridization studies described below. In some cases, recombinant plasmids have not yet been constructed and/or positively identified as representing a specific gene. To assess relative levels of connective tissue mRNAs in these situations, we are using the combined tools of cell free translation and immunoprecipitation. In addition, we are in the process of obtaining nucleic acid probes for these genes.

I. Molecular mechanism for the dedifferentiation of chondrocytes

Chondrocytes from chick embryo sterna are developmentally differentiated cells. They provide an advantageous system for studying the expression of co-ordinated genes since their phenotype can be experimentally altered by a variety of agents. As an approach toward understanding abnormal and normal cartilage development, we are examining the molecular basis for loss of phenotypic traits of chondrocytes after exposure to the thymidine analog 5-bromodeoxyuridine (BUdR). When grown in vitro, chondrocytes isolated from chick embryo sterna synthesize cartilage specific (predominantly chondroitin sulphate) proteoglycan, chondronectin (a chondrocyte attachment protein) and type II collagen. Upon exposure to BUdR the synthesis of these macro-molecules is blocked and the characteristic polygonal chondrocyte morphology is altered to a more fibroblastic one. These biochemical and morphologic changes are accompanied by an increase in the synthesis of both type I collagen and fibronectin. A correlation between cell morphology and mRNA profile has also been demonstrated. The mRNA for the core protein of cartilage proteoglycan disappeared at the same rate as the mRNA for pro- α 1(II) collagen. There was a concomitant increase in mRNA levels for pro- α 1(I)

and pro- $\alpha 2(I)$ collagen as well as for fibronectin. The data indicate that BUdR either directly or indirectly affects a pretranslational event in gene regulation.

We are in the process of quantifying the mRNA levels of several of the genes involved in the dedifferentiation process by both in vitro translation and by Northern hybridization. Recombinant DNA plasmids containing cDNA sequences for fibronectin and for pro- $\alpha 1(I)$ and pro- $\alpha 2(I)$ collagen have previously been constructed in the Laboratory of Molecular Biology, NCI. A cDNA clone derived from chick embryo sterna was also constructed in that laboratory. DNA sequence analysis (performed in collaboration with Drs. P. Fietzek and B. Olson, Rutgers Medical School) and hybridization studies indicate that the cDNA clone contains sequences complementary to pro- $\alpha 1(II)$ RNA collagen or to a collagen RNA that is co-regulated with type II collagen. In addition to definitively identifying the sternal cDNA clone, we are in the process of identifying the mRNA for chondronectin by in vitro translation and immuno-precipitation. Since we also have identified the in vitro translation product of the core protein of proteoglycan, we will be able to assess the relative quantities of all mRNA species involved in dedifferentiation by in vitro translation and/or hybridization. In the future we will determine if there is an alteration in the genome after BUdR-treatment which can explain the alteration in phenotypic expression of chondrocytes after BUdR-treatment.

II. Regulation of type I collagen synthesis with respect to the coordinate control of pro $\alpha 1(I)$ and pro $\alpha 2(I)$ synthesis

Type I collagen is the major protein component in bone, tendon and skin. The type I collagen molecule consists of three chains, two $\alpha 1(I)$ chains, and one $\alpha 2(I)$ chain, which are produced from large precursor forms called pro- α chains. Separate genes code for the pro- $\alpha 1(I)$ and pro- $\alpha 2$ chains. It is known that the rate of collagen synthesis can vary widely, being very high during development and wound repair. An imbalance in the ratio of $\alpha 1$ and $\alpha 2$ chains has been implicated in several human genetic disorders. We are trying to determine the mechanism used to control the synthesis of pro- $\alpha 1(I)$ and pro- $\alpha 2(I)$ chains.

We are studying two systems in which type I collagen synthesis is modulated. The first system utilizes chick embryo fibroblasts transformed by temperature-sensitive mutants of Rous sarcoma virus. These cells vary their collagen synthesis as a function of the permissive or restrictive temperature for the expression of the transforming protein p60^{src}. Both pro- $\alpha 1$ and pro- $\alpha 2$ mRNA levels followed the same time course during shifts to and from the permissive temperature, indicating that these two genes are coordinately controlled and that this phenomenon is regulated at the level of gene transcription or RNA stability.

Our recent studies have identified an alternate model system for studying coordinated $\alpha 1$ and $\alpha 2$ collagen gene expression, in which procollagen synthesis is modulated by the presence or absence of ascorbic acid in the medium used to maintain chick embryo calvaria in organ culture. The levels of translatable pro- $\alpha 1$ (I) and pro- $\alpha 2$ (I) RNAs from calvaria maintained for four days in the absence of ascorbic acid were decreased to 30% of control levels. Upon subsequent incubation of cultures for two days in the presence of ascorbic acid, levels of translatable pro- $\alpha 1$ (I) and pro- $\alpha 2$ (I) RNAs returned to normal.

We are currently preparing hybridization probes which are identical in size and specific activity to quantify the ratio of pro- $\alpha 1$ (I) and pro- $\alpha 2$ (I) mRNAs as they vary in both the temperature-sensitive and ascorbic acid-dependent systems. Such experiments will determine if the controlling step in coordinate regulation of collagen type I synthesis and the maintenance of the ratio of $\alpha 1$ and $\alpha 2$ chains is at the transcriptional level or at some other level of RNA processing or intracellular transport.

III. Molecular basis of altered collagen gene expression in myeloblastosis associated virus infected chick embryo fibroblasts.

Recent studies have shown that viral transformation alters the synthesis or processing of collagen. Viruses such as Rous sarcoma cause a decrease in collagen synthesis by transformed cells. As described above, the decrease in collagen synthesis in transformed chick embryo fibroblasts (CEF) is mediated through changes in type I collagen mRNA levels. In contrast, infection of chick fibroblasts by a subclone of myeloblastosis-associated virus (MAV) has recently been reported to cause an increase in collagen synthesis. MAV-infected CEF therefore offer an alternate model system for the study of collagen gene regulation. We have initiated studies to determine if the increase in collagen synthesis in MAV-infected CEF is due to an absolute increase in Type I collagen synthesis or if a switch in collagen type is involved. Additional studies will determine if this effect is reflected by an increase in the steady state level of collagen mRNAs. We are therefore characterizing the phenotype of MAV-infected chick fibroblasts and are establishing culture conditions to elicit a maximum change in collagen synthesis following infection by MAV. In the future, nucleic acids will be analyzed to determine the mechanism for altered collagen gene expression in MAV-infected cells.

IV. Characterization of the mRNAs coding for type IV collagen and laminin

Collagen type IV and laminin are basement membrane proteins. Although these proteins are often associated with each other, it is not clear if their genes are regulated in a coordinated fashion. In addition, each protein is itself composed of two distinct polypeptides. We have therefore initiated studies to identify and characterize the RNAs coding for type IV collagen and for laminin. Using RNA extracted from the EHS tumor, which produces large amounts of these materials, we discovered an inhibitor to translation in the low molecular weight RNA fractions. High molecular weight RNA fractions translate large proteins of the size expected for laminin and type IV

collagen. We are in the process of identifying these translation products by immunoprecipitation. We are also utilizing several cell lines grown in vitro which synthesize type IV collagen and laminin. In the future, we hope to construct and clone cDNAs for the several mRNAs which encode the type IV and laminin gene products, thus providing tools for further investigations of the control of the genes for these important basement membrane proteins.

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SUMMARY OF WORK (200 words or less - underline keywords) <p>The purpose of this project is to study the <u>structure</u> and <u>function</u> of the <u>extracellular matrix</u>. Particular attention is directed toward (1) understanding the interaction of the <u>attachment factor</u>, fibronectin, with collagen and (2) determining the role of the resulting fibronectin-collagen complex on cell behavior including <u>adhesion</u>, <u>migration</u>, and <u>differentiation</u>. (3) The interaction of other attachment factors, including laminin and chondro-nectin, with collagen and proteoglycans is being investigated.</p>																				

Methods. The interaction of fibronectin with collagen and the adhesion of cells to collagen are studied in vitro. Cell migration is studied using a Boyden chamber equipped with collagen-coated filters. Collagens and fibronectin are prepared by standard methods while cells are obtained either as cell lines or from tissues after proteolytic dissociation. Human skin fibroblasts and CHO cells were obtained from American Type Culture Collection, 3T3 and NRK cells from S. Aaronson (NCI), smooth muscle cells from sheep embryonic aorta, and Schwann cells (from rat dorsal root ganglia) from M. DuBois-Dalcq (NINCDS).

Introduction and Objectives - Many cells exist surrounded by a collagenous matrix. The role of collagen in the tissue is probably more than structural since collagen matrices promote the adhesion, growth, and differentiation of cells. Each tissue contains unique matrix proteins which determine which cell will populate the tissue and how the cells will express their phenotype. Fibroblastic cells do not bind directly to collagen but are linked to the collagen by fibronectin. Cartilage lacks fibronectin and chondrocytes utilize another factor, chondronectin, for adhesion. We are currently investigating the interaction of fibronectin with native collagen and the role of the fibronectin-collagen complex in mediating the attachment and migration of various cell types. Our studies indicate that the interaction of fibronectin with collagen and with the cells is specific and is important for the adhesion and migration of many cells particularly in development and wound healing.

Interaction of fibronectin and other matrix proteins with native collagens - Studies on the nature of the interaction of fibronectin with native collagen have been carried out. From studies with denatured collagen, we previously demonstrated that a specific sequence of approximately 8 amino acids on the collagen $\alpha 1(I)$ chain is recognized by fibronectin. Likewise a specific 40,000 dalton fragment of fibronectin has been found to contain the collagen binding site. Ultrastructural studies by Furcht suggest that fibronectin binds to native collagen fibrils in a regular array. We find that fibronectin delays the formation of collagen fibrils confirming that it binds to native collagen. In addition, the 40,000 dalton fragment of fibronectin which binds to collagen was as active as fibronectin itself on a molar basis in delaying fibril formation. Other fragments of the fibronectin molecule (160,000 dalton cell binding fragment) and other proteins, including albumin, laminin, chondronectin, and link protein, were inactive. Denatured collagen containing the fibronectin binding site blocked the fibronectin inhibition of fibrillogenesis. These data demonstrate that fibronectin binds to native collagen at the same site as previously reported for denatured collagen. Since fibronectin can bind to collagen and influence the rate of fibril formation, it may have a role in vivo in determining fibril size and structure.

Similar studies are being carried out with type II collagen to determine the factors which regulate fibril formation. In preliminary studies, proteoglycans (which are abundant in the extracellular matrix of cartilage) appear to regulate the rate and extent of fibril formation. Such studies should

provide information about macromolecules which interact with collagen to form the extracellular matrix.

The interaction of laminin with collagens is being investigated. It has recently been shown (Terranova et al., Cell 22: 719, 1980) that various epithelial cells bind preferentially to Type IV collagen via the glycoprotein laminin. Using a modified antigen-antigen binding assay with ELISA technique, we find laminin binds preferentially to type IV collagen over the other collagen types. Laminin also binds to the heparan sulfate proteoglycan of basement membrane. How the laminin, collagen and proteoglycan interact to form the basement will also be investigated in fibril studies.

A bone-specific protein, termed osteonectin, has been found to bind selectively to both collagen and hydroxyapatite. The osteonectin-collagen complex can bind free calcium ions and nucleate mineral phase from metastable balanced salt solutions. Since this protein is localized to mineralized bone trabeculae in the extracellular matrix, it may be active in initiating mineralization and binding hydroxyapatite crystals to bone collagen.

Wilkes, Martin, Chandrasekhar, Woodley, Kleinman, Termine

The interaction of fibronectin with the cell surfaces and with gangliosides - Although the cells are cultured in a 10-fold excess of fibronectin (in serum), greater than 80% of the fibronectin on the cell surface originates from the cells. Soluble collagen stimulates the binding of fibronectin to the cell surface 2- to 6-fold in a concentration- and time-dependent manner. Cells maintained in suspension bind much less fibronectin than cells in monolayer. In the presence of soluble collagen, cells in suspension bind 2- to 6-fold more fibronectin. Gangliosides, which have previously been shown to inhibit fibronectin-mediated cell adhesion (Kleinman et al., 1979. Proc. Natl. Acad. Sci. USA 76: 3367-3371), also block the binding of fibronectin to the cell surface even in the presence of soluble collagen. These data demonstrate that the fibronectin present in the cell layer originates from the cells and that collagen facilitates the incorporation of fibronectin into the cell layer. Such data may explain why transformed cells, which synthesize reduced amounts of collagen, also have reduced amounts of fibronectin in the cell layer.

Specific complex gangliosides (GD_{1a}, GT₁) bind to fibronectin and block cell adhesion. The specificity of the interaction of fibronectin with GD_{1a} has been confirmed in studies with other lipids and glycolipids. The agglutination of red blood cells by fibronectin is also blocked by the same gangliosides that block cell adhesion. Such studies confirm that fibronectin binds gangliosides and suggests that the cell surface receptor for fibronectin is a ganglioside. Since complex gangliosides are reduced on the surface of transformed cells, it is possible this reduction also contributes to the loss of fibronectin from the surfaces of transformed cells.

Rennard, Wind, Hewitt, Grotendorst, Kleinman

Migration of cells on collagen substrates - Fibroblasts have been shown to migrate in the Boyden chamber on filters coated with collagen. In this system, fibronectin is a potent chemoattractant for fibroblasts, Schwann cells, and smooth muscle cells and the cell binding fragment of fibronectin ($M_r=160,000$) contains all the biological activity.

Adhesion and migration studies with smooth muscle cells have revealed that these cells use fibronectin to adhere to type I collagen but these cells can adhere to Type V in the absence of any added factors. Furthermore, preincubation of these cells with soluble type V collagen blocks their subsequent adhesion to type V collagen while preincubation with type I has no effect. A cell surface carbohydrate-containing component appears to be the collagen type V receptor as determined using enzymatic and lectin treatments of the cells. The growth factor released from platelets (PDGF) is a chemoattractant for smooth muscle cells as well as 3T3 and NRK cells. Other growth and stimulatory factors, such as FGF, NGF, EGF, and insulin, do not influence cell migration. The effect of PDGF on cell migration is distinct from its mitogenic activity since (1) the migration response occurs rapidly (2-4 hrs), while the cells only divide after 24 hours, (2) PDGF is active for migration at concentrations below those required for cell division, and (3) migration is not affected by inhibitors of DNA synthesis. However, inhibitors of both RNA and protein synthesis block migration suggesting that the synthesis of new proteins is required for cell migration to PDGF. Cells pretreated with PDGF, rapidly growing cells (log phase) and transformed cells are not as responsive to PDGF as growth-arrested cells.

Such studies demonstrate that fibroblasts and smooth muscle cells could migrate to sites of injury in response to fibronectin and PDGF where the cells would subsequently proliferate and repair and replace the damaged tissue. Repetition of this repair process could lead to pathological conditions such as the formation of the atherosclerotic plaque after repeated endothelial cell injury.

In the case of Schwann cells, fibronectin not only stimulates migration but also stimulates cell division. Schwann cells normally divide poorly and generally require factors, such as c-AMP, cholera toxin and pituitary extract, in order to proliferate. Fibronectin at 10 $\mu\text{g/ml}$ is as potent as these factors combined in stimulating Schwann cell growth. In vivo fibronectin may also have a role in wound repair by stimulating both migration and proliferation.

"
Grotendorst, Seppa, Schiffmann, Martin, Kleinman

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Gauss-Muller, V., Kleinman, H.K., Martin, G.R., and Schiffmann, E.: Role of attachment and attractants in fibroblast chemotaxis. J. Lab. Clin. Med. 96: 1071-1080, 1980.

Kleinman, H.K. and Wilkes, C.M.: Interaction of fibronectin with collagen. In Weiss, J.B. and Jaysen, M.I.V. (Eds.): Collagen in Health and Disease. Churchill Livingstone. In press, 1981.

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Brown, K.S., Cranley, R.E., Greene, R., Kleinman, H.K., and Pennypacker, J.P.: Disproportionate micromelia (Dmm): an incomplete dominant mouse dwarfism with abnormal cartilage matrix. J. Embryol. exp. Morph., 62: 165-182, 1981.

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Termine, J.D., Kleinman, H.K., Witson, S.W., Conn, K.M., McGarvey, M.L., and Martin, G.R.: Osteonectin, a bone-specific protein linking mineral to collagen. Cell, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 0253-04 DB
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Development of cartilage		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Varner, H.H. Arias, S. Hewitt, A.T. Lee, W.A. Silver, M.H.	Postdoctoral Fellow Guest Worker NIH Expert Chemist Postdoctoral Fellow	DB NIDR DB NIDR DB NIDR DB NIDR DB NIDR
COOPERATING UNITS (if any) NCI, NIH		
LAB/BRANCH Laboratory of Developmental Biology & Anomalies		
SECTION Connective Tissue Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland		
TOTAL MANYEARS: 4.90	PROFESSIONAL: 2.75	OTHER: 2.15
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords)		
<p>The factors influencing <u>chondrogenesis</u> are under study. Particular attention is being directed toward the <u>extracellular matrix</u> of developing <u>cartilage</u> and its relationship to normal cellular function. Two types of factors are being characterized: those which stimulate chondrocyte attachment and stimulate chondrogenesis of limb mesenchyme; and those which perturb the phenotype of <u>chondrocytes</u>.</p> <p>In these investigations, use is being made of limb bud mesenchyme cell cultures and mature <u>chondrocytes</u> in culture.</p>		

Chondronectin as an adhesion factor for chondrocytes - We have previously reported (Hewitt et al., Proc. Natl. Acad. Sci. USA, 77: 385-388, 1980) that chondrocyte attachment is mediated by chondronectin, a glycoprotein which is present in serum, in cartilage, in the matrix of a chondrosarcoma, and in vitreous fluid. Its molecular weight based on migration on SDS gels is 180,000 while sedimentation equilibrium analyses give a value of 172,000. The molecule is comprised of disulfide-linked chains with an apparent molecular weight of 70,000 daltons. Chondronectin is approximately 7% carbohydrate. Two "species" of the molecule were separated by preparative isoelectric focusing with pI's of 4.6 and 6.8. Chondronectin is very resistant to digestion by proteases in comparison to fibronectin and laminin and the fragments obtained from the three proteins by peptide mapping are distinct. Current studies suggest that chondronectin is a compact globular molecule.

A quantitative immunoassay for chondronectin has been developed. Antibodies against chondronectin do not cross-react with either fibronectin or laminin. Antibodies against chondronectin inhibit the attachment of chondrocytes to type II collagen. Indirect immunofluorescence studies show that chondronectin is concentrated pericellularly, a location consistent with its function as an attachment protein rather than as a matrix protein.

It became apparent during our early studies that chondronectin does not bind readily to collagen and might require interaction with some other component of cartilage as well. We noted that compounds that inhibited the glycosylation of proteoglycan, such as xylosides, inhibited chondrocyte attachment to collagen substrates. Substrates composed of cartilage proteoglycan and collagen bind chondronectin and allow chondrocytes to attach. We also found that chondronectin can be purified from serum by columns composed of cartilage proteoglycan-Sepharose. These results demonstrate that chondronectin binds to cartilage proteoglycan and then to cartilage collagen.

Studies are currently underway to establish the role of chondronectin in cartilage development. These studies have shown that spot cultures of embryonic chick limb mesenchymal cells are stimulated to form cartilage by exogenous chondronectin while antibodies to chondronectin inhibit chondrogenesis. Both effects are dose dependent. These studies suggest that the interactions between chondronectin and other cartilage components are important both for the development and for maintenance of cartilage. The mechanism of chondronectin's effect on cartilage differentiation and its function in various pathological conditions including chondrodystrophies will be investigated.

Hewitt, Varner, Silver, Hassell, Horigan

Antibodies to collagen II and to chondronectin in serum and joint fluid of arthritic mice and humans - In spontaneous and experimental arthritides with joint destruction, several components of the cartilage matrix might induce autoantibodies. The presence of antibodies against collagen type II

and chondronectin in serum from arthritic mice and in serum from patients with relapsing polychondritis, Reiter's syndrome, Lyme disease and juvenile rheumatoid arthritis was tested by ELISA. Serum from forty percent of the mice showed low titers against chondronectin and 10% showed titers against type II collagen, although there was no association between them. Attempts to confirm the presence of antichondronectin antibody by immunofluorescence with embryonic cartilage were negative. While 40% of the human samples contained anti-type II collagen antibody, a pseudo-positive unspecific reaction against chondronectin was present in all sera, which was not reduced by the addition of bovine serum albumin at concentrations as high as 6 mg/ml. The nature of this reaction remains to be established. It should be noted that in the initial murine tests, ELISA plates were coated with chicken chondronectin. Subsequent analyses have shown that interspecies cross-reactivity is poor which could account for the inconclusive results. Studies are currently in progress to test samples using human chondronectin as antigen.

Arias

Studies on chondrogenic expression in vitro - We have isolated a protein present in certain commercial preparations of bovine testicular hyaluronidase which causes a reversible inhibition of chondrogenic expression in vitro. Following purification by chromatofocusing, the active component was found to have a molecular weight of 150,000 as determined by SDS-PAGE and gel filtration and to be composed of disulfide-linked chains ($M_r=75,000$). The factor is sensitive to proteolysis by trypsin and is stained by the periodic acid-Schiff reagent indicating that it is a glycoprotein. Hyaluronidase activity is not detectable in the purified protein. When added to embryonic chick sternal chondrocytes at 4 $\mu\text{g/ml}$, the protein causes the cells to elongate and assume a fibroblastic morphology within 48 hours. Decreased sulfate incorporation into proteoglycan, a switch in collagen synthesis from type II to type I, and the suppression of proteoglycan core protein synthesis are found by 96 hours. The protein also inhibits chondrogenesis in cultures of limb bud mesenchyme at 1 $\mu\text{g/ml}$ and at higher levels (4 $\mu\text{g/ml}$) inhibits myotube formation by cultured myoblasts but is not toxic for these cells. Additional studies are in progress to determine whether other cells in culture are affected by the protein and to further characterize the mechanism by which chondrogenesis is inhibited.

Varner, Hewitt, Hassell, Horigan, and Grotendorst

PUBLICATIONS:

Kleinman, H.K., Hewitt, A.T., Grotendorst, G.R., Murray, J.C., Rohrbach, D.H., Terranova, V.P., Rennard, S.I., Varner, H.H., and Wilkes, C.M.: Role of matrix components in adhesion and growth of cells. In Pratt, R.M. and Christiansen, R.L. (Eds.): Current Research Trends in Prenatal Craniofacial Development. New York, Elsevier-North Holland, 1980, pp. 277-295.

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Kleinman, H.K., Rohrbach, D.H., Terranova, V.P., Varner, H.H., Hewitt, A.T., Grotendorst, G.R., Wilkes, C.M., Martin, G.R., Seppa, H., and Schiffmann, E.: Collagenous matrices as determinants for cell function. In Furthmayr, H. (Ed.): Immunochemistry of the Extracellular Matrix, Vol. II: Applications. Cleveland, CRC Press, in press.

Hewitt, A.T., Varner, H.H., Silver, M.H., Wilkes, C.M., and Martin, G.R.: Isolation and partial characterization of chondronectin, an attachment factor for chondrocytes. J. Biol. Chem., in press.

Hewitt, A.T., Kimata, K., Pennypacker, J.P., Wilkes, C.W., Martin, G.R., and Kleinman, H.K.: The attachment of chondrocytes and fibroblasts to collagen. Second Munich Symposium on Connective Tissue, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00275-03 DB						
PERIOD COVERED October 1, 1980 - September 30, 1981								
TITLE OF PROJECT (80 characters or less) Biological testing of fluoride								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%;"> <tr> <td style="width: 33%;">Martin, G.R.</td> <td style="width: 33%;">Ch, Lab. Dev. Bio. & Anomalies</td> <td style="width: 33%;">DB NIDR</td> </tr> <tr> <td>Brown, K.S.</td> <td>Medical Director</td> <td>DB NIDR</td> </tr> </table>			Martin, G.R.	Ch, Lab. Dev. Bio. & Anomalies	DB NIDR	Brown, K.S.	Medical Director	DB NIDR
Martin, G.R.	Ch, Lab. Dev. Bio. & Anomalies	DB NIDR						
Brown, K.S.	Medical Director	DB NIDR						
COOPERATING UNITS (if any) University of Minnesota; Litton Bionetics; and NCI, NIH								
LAB/BRANCH Laboratory of Developmental Biology & Anomalies								
SECTION Connective Tissue Section								
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland								
TOTAL MANYEARS: .10	PROFESSIONAL: .10	OTHER: 0.00						
CHECK APPROPRIATE BOX(ES) <table style="width: 100%;"> <tr> <td><input type="checkbox"/> (a) HUMAN SUBJECTS</td> <td><input type="checkbox"/> (b) HUMAN TISSUES</td> <td><input checked="" type="checkbox"/> (c) NEITHER</td> </tr> <tr> <td colspan="3"> <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </td> </tr> </table>			<input type="checkbox"/> (a) HUMAN SUBJECTS	<input type="checkbox"/> (b) HUMAN TISSUES	<input checked="" type="checkbox"/> (c) NEITHER	<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
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<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) <p>The purpose of this project is to study the <u>action</u> of <u>fluoride</u> in various systems used to detect clastogenic or mutagenic substances. To date fluoride has been examined in several systems used to detect mutagens and found to be <u>non mutagenic</u>. No effects on chromosome structure were noted in animals given widely different levels of fluoride. DNA repair after X-ray was unchanged by fluoride. No genetic effects of fluoride were noted in a recessive lethal test of fluoride on drosophila. The data indicate that fluoride has no mutagenic activity. Ongoing studies and reports of fluoride effects on metabolism and growth in the literature are being monitored.</p>								

Fluoride has been widely used to suppress caries. At the levels recommended (0.5-1 ppm), no detrimental effects of fluoride on the health of individuals have been noted. At very high fluoride intakes, alterations in bone metabolism can occur and are associated with degenerative changes in bone.

It is the purpose of this project to examine fluoride in some of the more recently developed tests which detect mutagenic or clastogenic activity. Considerable epidemiological data indicate that fluoride consumption does not increase the incidence of cancer or birth defects. The tests described below provide corroborative experimental information.

In our initial studies, we measured the numbers of abnormal chromosomes in mice from colonies raised on very different levels of fluoride. Bone levels of fluoride differed some 450 fold. The rate of sister chromatid exchange was similar in animals from the two groups. Mice given low (1 ppm) to high levels (100 ppm) of fluoride had similar levels of chromosomal abnormalities which did not differ from the level of abnormalities present in animals receiving no fluoride supplement.

A repeat of the study of mouse bone marrow, testing chromosomes after six weeks of treatment with a range of 0-100 ppm fluoride in water and using sample numbers sufficiently large to detect a doubling of the rate of chromosome malformations confirmed the earlier study that no change in chromosome abnormality rate was produced by these levels of fluoride.

Slight and not statistically significant increases in XY chromosomal dissociation were noted in the range 2-4% in animals supplemented with fluoride. Great variations in this parameter (up to 40%) have been noted in previously published studies and the XY chromosome dissociation is believed to arise during preparation of the chromosomes for examination.

No effect of fluoride levels was found in a sex-linked recessive lethal test in *Drosophila melanogaster*. This is an in vivo test in an eukaryotic organism which measures the frequency of mutation of approximately 1000 loci on the X-chromosome. It has been used as an effective assay for many mutagens.

Fluoride was found to be non mutagenic in the Ames test using microbial cells in vitro. It was found to have no effect on the ability of mouse leukemia cells to repair x-ray produced damage.

Taken together the data show no genetic or mutagenic actions of fluoride.

Literature surveys of reported effects of fluoride on cell metabolism and biochemistry in vivo and in vitro are being carried out at semiannual intervals. Ongoing studies of possible fluoride effects by the National Toxicology Program and National Cancer Institute are also being followed for possible suggestions for additional tests.

PUBLICATIONS:

None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00149-07 DB																								
PERIOD COVERED October 1, 1980 - September 30, 1981																										
TITLE OF PROJECT (80 characters or less) Growth and differentiation during craniofacial development																										
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Hassell, J.</td> <td style="width: 33%;">Research Biologist</td> <td style="width: 33%;">DB NIDR</td> </tr> <tr> <td>Cannon, F.B.</td> <td>Bio Lab Tech (Micro)</td> <td>DB NIDR</td> </tr> <tr> <td>Horigan, E.A.</td> <td>Research Biologist</td> <td>DB NIDR</td> </tr> <tr> <td>Kleinman, H.K.</td> <td>Research Chemist</td> <td>DB NIDR</td> </tr> <tr> <td>Leyshon, W.C.</td> <td>Biologist</td> <td>DB NIDR</td> </tr> <tr> <td>Mosley, G.L., Jr.</td> <td>Bio Lab Tech (Animal)</td> <td>DB NIDR</td> </tr> <tr> <td>Chandrasekhar, S.</td> <td>Visiting Fellow</td> <td>DB NIDR</td> </tr> <tr> <td>Woodley, D.T.</td> <td>Expert</td> <td>DB NIDR</td> </tr> </table>			Hassell, J.	Research Biologist	DB NIDR	Cannon, F.B.	Bio Lab Tech (Micro)	DB NIDR	Horigan, E.A.	Research Biologist	DB NIDR	Kleinman, H.K.	Research Chemist	DB NIDR	Leyshon, W.C.	Biologist	DB NIDR	Mosley, G.L., Jr.	Bio Lab Tech (Animal)	DB NIDR	Chandrasekhar, S.	Visiting Fellow	DB NIDR	Woodley, D.T.	Expert	DB NIDR
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TOTAL MANYEARS: 6.15	PROFESSIONAL: 1.75	OTHER: 4.40																								
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SUMMARY OF WORK (200 words or less - underline keywords) The purpose of this project is to understand the regulation of <u>cellular proliferation</u> and <u>differentiation in craniofacial</u> tissues and in other tissues undergoing similar developmental events. At present we are refining an in vitro method for screening <u>teratogens</u> , and determining the role of extracellular matrix materials in <u>chondrogenesis</u> . We are also isolating proteins associated with proteoglycans and determining their interaction with other connective tissue components.																										

I. Teratogen Screening

Previously, we suggested the use of the developing limb bud culture as an in vitro test system for detecting teratogens. Various drugs when added to mouse or chick limb bud cells inhibit their differentiation into chondrocytes. This system has been improved in terms of sensitivity and simplicity. The cells are now cultured in multi-well culture plates requiring only small amounts of media and test compound. The cells are cultured for 6 days enabling us to evaluate substances that effect differentiation, as well as, those that effect cartilage matrix production. At the end of the culture period the staining of sulfated proteoglycans with alcian blue is used as a measure of cartilage matrix formation. The dose necessary to reduce staining 50% is used to estimate a drug's teratogenic potential (TP₅₀).

In addition, we have developed a one day test for teratogens using cultures of chick sternal chondrocytes plated out at high density. By using microtiter plates (requiring 0.2 ml media), the cells can be cultured, stained, and quantitated all in the same dish.

It is possible with either test systems to assay serum from animals after drug administration for the presence of metabolites. We plan to develop a system in which limb bud or sternal cells are co-cultured with human liver cells in order to allow the production of teratogenic metabolites in vitro.

Using these systems we have examined several suspected human teratogens. Hexachlorophene, a once widely used antibacterial agent, produces skeletal defects in embryonic rats. It is active at 0.25 µg/ml in the limb bud and 10 µg/ml in the sternal assay. Furthermore, serum from animals receiving hexachlorophene blocks the differentiation of cultured cells. Bendectin, an antinausea medication used for morning sickness, was not found to produce malformations when administered to mice at levels up to 80 mg/kg. We are currently testing this drug in primates. In the in vitro assays Bendectin was found to have a TP₅₀ of 100 µg/ml and therefore have questionable activity in this in vitro test.

No teratogenic activity has been detected with Thalidomide in mice or in the in vitro systems. It is intended to test serum from individuals on Thalidomide medication for teratogenic activity.

Hassell, Horigan and Mosley

II. Chondrogenesis

Cartilage formation regulates the growth of many craniofacial structures, in particular the mandible or lower jaw. We have evaluated the effect of extra-cellular matrix materials on chondrogenesis by adding various materials directly to the media of developing limb bud cell cultures. The effect of these materials on chondrogenesis is assessed by staining the cultures for cartilage proteoglycan deposition with alcian blue. Chondronectin enhances chondrogenesis. Fibronectin enhances chondrogenesis when given early during

the culture period and inhibits chondrogenesis when given late in the culture period. Antifibronectin antibodies inhibit when given early and stimulate when given late. The addition of heparan sulfate proteoglycan or antibodies to this proteoglycan does not alter chondrogenesis. These observations indicate that certain extracellular matrix components are involved in the initial steps in chondrogenesis while others affect later steps.

Horigan, Hewitt, and Varner

III. Proteoglycan associated proteins

The cartilage link protein has been shown to stabilize the interaction of cartilage proteoglycan with hyaluronic acid. We have investigated the possibility that link protein may be present in non-cartilagenous tissues, such as sclera, cornea and aorta. The presence of link protein in these tissues was established by histological studies with antibodies specific to link protein and by showing that extracts from metabolically labeled specimens contain a protein that binds to the cartilage proteoglycan and is the same size as cartilage link. The scleral extracellular matrix contains proteoglycans that do not interact with link and we speculate that the link proteins present in this tissue, and perhaps other tissues as well, are interacting with some other component. We have also found that link protein binds to type I collagen by ELISA and can be selectively purified from tissue extracts by chromatography on Sepharose-collagen columns. The results of these studies suggest that cartilage link protein may stabilize interactions other than proteoglycan-hyaluronic acid.

The EHS sarcoma was found not to contain cartilage link type proteins and we have initiated studies to isolate the protein(s) which associate with the proteoglycan present in the tissue, the heparan sulfate proteoglycan. By using standard associative and dissociative CsCl gradients we have isolated a protein of $\sim 60,000$ MW that binds to the heparan sulfate proteoglycan. This protein may represent a new class of "link" type proteins.

Cannon, Chandrasekhar, Kleinman, Leyshon, Woodley

PUBLICATIONS:

Greene, R.M., Shanfeld, J.L., Davidovitch, Z., and Pratt, R.M.: Immunohistochemical localization of cyclic AMP in the developing rodent secondary palate. J. Embryol. exp. Morphol. In press, 1981.

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Pratt, R.M., Yoneda, T., Silver, M.H., and Salomon, D.S.: Involvement of glucocorticoids and epidermal growth factor in secondary palate development. In Pratt, R.M. and Christiansen, R.L. (Eds.): Current Research Trends in Prenatal Craniofacial Development. New York, Elsevier North-Holland, 1980, pp. 235-252.

Salomon, D.S. and Pratt, R.M.: Glucocorticoid receptors and cleft palate in the mouse. In Pratt, R.M. and Christiansen, R.L. (Eds.): Current Research Trends in Prenatal Craniofacial Development. New York, Elsevier North-Holland, 1980, pp 367-386.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00257-03 DB															
PERIOD COVERED October 1, 1980 - September 30, 1981																	
TITLE OF PROJECT (80 characters or less) Migration and differentiation of cranial neural crest cells																	
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Greenberg, J.H.</td> <td style="width: 33%;">Senior Staff Fellow</td> <td style="width: 33%;">DB NIDR</td> </tr> <tr> <td>Jerdan, J.A.</td> <td>Postdoctoral Fellow</td> <td>DB NIDR</td> </tr> <tr> <td>Vogel, D.</td> <td>Biol. Lab. Tech.</td> <td>DB NIDR</td> </tr> <tr> <td>Goldsher, V.</td> <td>Biologist</td> <td>DB NIDR</td> </tr> <tr> <td>Beckwith, C.</td> <td>Biological Aid</td> <td>DB NIDR</td> </tr> </table>			Greenberg, J.H.	Senior Staff Fellow	DB NIDR	Jerdan, J.A.	Postdoctoral Fellow	DB NIDR	Vogel, D.	Biol. Lab. Tech.	DB NIDR	Goldsher, V.	Biologist	DB NIDR	Beckwith, C.	Biological Aid	DB NIDR
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SECTION Craniofacial Development Section																	
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SUMMARY OF WORK (200 words or less - underline keywords) <u>Cranial neural crest cells</u> migrate in highly specific pathways in the embryo and differentiate into many craniofacial structures. In an approach toward characterizing the factors which specify the migratory pathways, we are examining the interactions of these cells in vitro with the extracellular matrix molecules, <u>collagen</u> and <u>fibronectin</u> , which surround the migratory cells. We are also examining possible <u>chemotactic responses</u> of the neural crest cells to a variety of <u>growth factors</u> . Neural crest cells cultured in the presence of calf serum differentiate into <u>melanocytes</u> . We have isolated a factor from calf serum which promotes melanogenesis of neural crest cells and of a <u>melanoma</u> cell line.																	

INTRODUCTION:

The neural crest is composed of a pluripotent population of cells which migrate extensively in the early embryo and then differentiate into a variety of phenotypes, including melanocytes, neurons, and connective tissue cells. Over the last several years we have developed systems for growing chick cranial neural crest cells in culture. Under appropriate conditions the cells differentiate reproducibly into either melanocytes or cholinergic neurons. Cell culture has made it possible to examine certain factors which affect normal differentiation, as well as drugs which disrupt development. We have also used cell culture as a means to obtain sufficient quantities of neural crest cells to study the mechanisms that direct the cells to migrate in highly specific patterns.

This report describes our current research on the role of extracellular matrix macromolecules and growth factors in the migration of neural crest cells and the isolation and purification of a serum factor which promotes melanogenesis of these cells. In addition, we have used melanoma cells as a model to investigate serum factors which promote melanogenesis.

I. Role of collagen and fibronectin in migration of neural crest cells

During early embryogenesis, neural crest cells migrate through a matrix rich in collagen, glycosaminoglycans and glycoproteins. We have examined the attachment of cultured neural crest cells to collagen substrates of types I-V. The cells attach equally well to all types of collagen in the presence, but not in the absence, of serum. Purified fibronectin, but not chondro-nectin or laminin, can substitute for serum in promoting attachment to collagen. Although neural crest cells do not synthesize fibronectin, protein synthesis is required for optimal attachment. This suggests that the cells may synthesize a receptor for fibronectin or may utilize an endogenous factor in addition to fibronectin.

We then investigated the possibility that chemotaxis plays a role in directing the migration of neural crest cells. Neural crest cells grown in culture were assayed in microwell Boyden chambers for their migration through gelatin-coated Nuclepore filters in response to fibronectin. Fibronectin stimulates both directed migration (chemotaxis) and random motility in a concentration-dependent manner. Proteolytic fragments of fibronectin were tested for their chemotactic activity, and we found that the cell-binding fragment (MW=150,000), but not the collagen-binding (MW=40,000) or heparin-binding (MW=50,000) fragments, stimulates chemotaxis.

These results suggest that in the embryo some neural crest cells attach to collagen by means of fibronectin and that local differences in concentration or availability of fibronectin could promote haptotaxis, or the movement from a less adhesive to a more adhesive substrate. Alternatively, a gradient of fibronectin or its degradation products released from sites along the migration pathway could recruit neural crest cells by chemotaxis.

Vitamin A is a teratogen which causes cleft palate and other defects and which we have found disrupts neural crest migration in the embryo. Since we observed that preincubation of neural crest cells with vitamin A enhances fibronectin-mediated attachment to collagen, we tested its effect on migration. Preincubation of cells with vitamin A stimulates migration in response to fibronectin, but vitamin A alone is not a chemoattractant. Although increased migration is in contrast to what would be expected from in vivo experiments, it appears that vitamin A may exert its teratogenic effect by directly altering the adhesive properties of neural crest cells.

" "

Greenberg, Seppa, Seppa, and Hewitt

II. Chemotaxis of neural crest cells in response to growth factors

It is likely that factors in addition to fibronectin may be chemoattractants for neural crest cells and, unlike fibronectin whose distribution is widespread, may be more highly localized in specific regions of the embryo.

In order to test for the chemotactic effect of molecules in the absence of gelatin and fibronectin, it was necessary to develop a method to promote attachment of neural crest cells to the Nuclepore filters used in Boyden chamber assays. We have found that treatment of the filters with poly-ornithine allows excellent cell attachment, and we have used poly-ornithine-treated filters for subsequent assays.

Preliminary experiments have shown that fibroblast growth factor is an attractant for neural crest cells, with 50 ng/ml causing significant migration. We have also observed that certain preparations of a pigmentation-promoting factor from calf serum (see below) stimulate migration. Epidermal growth factor, nerve growth factor, and platelet-derived growth factor were not active. Trials are continuing with other compounds, including melanocyte-stimulating hormone and tumor promoters.

Greenberg

III. Melanogenesis of cultured neural crest cells

Cultured neural crest cells differentiate into cholinergic neurons in medium containing horse serum and into melanocytes in medium containing calf serum. The extent of melanogenesis is dependent on the concentration of calf serum. These findings are consistent with the idea that specific factors in sera promote differentiation into each of the phenotypes.

Pigmentation has been assayed by measuring the incorporation of ^{14}C -tyrosine into trichloroacetic acid-insoluble material in the presence and absence of phenylthiourea, a specific inhibitor of tyrosinase. The 40-60% ammonium sulfate cut of calf serum was chromatographed on dye affinity columns. The material which did not bind to Amicon Blue A but did bind to Blue B was further purified by chromatography on hydroxyapatite. A single active peak was eluted from this column and was enriched approximately 1200-fold

in pigmentation-promoting activity. It is likely that additional steps are required to purify the material, since some preparations contain several peptide bands. The pigmentation-promoting factor (PPF) is trypsin-sensitive and stable to heating at 56° for 30 min.

Antibodies to PPF were raised in rabbits. ELISA assays have demonstrated a high titer of PPF in calf serum and in fetal and adult bovine sera, as well as in human serum and chicken serum. Horse serum contained no PPF, and the antibody does not react with α - or β -MSH.

Jerdan, Varner, and Greenberg

IV. Differentiation of melanoma cells

B16/C3 murine melanoma cells grown at low density synthesize low levels of melanin. Increasing the concentration of serum induces melanogenesis. We have carried out preliminary studies on these cells in order to compare their serum-stimulated melanogenesis with that previously observed in neural crest cultures. We found that, as in the case of neural crest cells, serum stimulated incorporation of ^{14}C -tyrosine into melanin but not into protein. The effect was dependent upon the serum concentration. Furthermore, the pigmentation-promoting factor for neural crest cells isolated from calf serum stimulated melanogenesis of B16/C3 cells.

Electron microscopy of B16/C3 cells demonstrated the presence of premelanosomes in all cells, suggesting that serum stimulates a late stage of melanogenesis, such as tyrosinase synthesis or activation. Studies are continuing to compare the differentiation of neural crest and B16/C3 cells. B16/C3 cells, which are available in large quantities, may serve as a useful model in which to identify and purify factors which affect melanogenesis in the embryo.

Greenberg and Jerdan

FUTURE PLANS

Future experiments will continue to define the role of other matrix components in neural crest cell migration. In particular, various glycosaminoglycans will be tested for their ability to modulate attachment and migration of the cells, using the systems that we have previously described, and experiments will be conducted in vivo to test the effects of exogenous fibronectin and anti-fibronectin antibodies injected locally at the time of neural crest migration. Studies will also continue on the role of growth factors in migration and to determine if chemotactically active factors have an effect on differentiation of these cells.

The pigmentation-promoting factor from calf serum will be purified to homogeneity by electrofocusing. Antibodies to PPF will be used to inhibit melanogenesis in vitro and for immunofluorescence localization of PPF-like molecules in the early embryo. ELISA assays will be used to detect the distribution of PPF in fetal calf tissues, which may serve as a richer

source of the factor. Iodinated PPF will be used to determine if PPF receptors are present on the surface of neural crest and melanoma cells. Since the extent of differentiation appears to be inversely related to the metastatic potential of melanoma cells, we will test the effect of PPF on the ability of malignant melanoma cells to metastasize.

PUBLICATION:

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ANNUAL REPORT OF THE LABORATORY OF ORAL MEDICINE
NATIONAL INSTITUTE OF DENTAL RESEARCH
1980 - 1981

The Laboratory of Oral Medicine is concerned with the etiology and pathogenesis of diseases of the soft tissue of the oral cavity with emphasis on: (1) viral infections such as herpes simplex virus; (2) aphthous ulcers and other dermatologic disorders; (3) exocrine (salivary glands) and endocrine (pancreas) diseases with special emphasis on diabetes mellitus; and (4) premalignant and malignant lesions of the oral cavity. The program is disease oriented and highly interdisciplinary. The Laboratory is made up of investigators who are trained in a variety of disciplines including virology, immunology, pathology, cell biology, molecular biology and clinical medicine and dentistry.

Over the last year, in-depth studies have continued on the projects discussed in previous annual reports. Two new projects have been initiated. The first concerns hybridomas to make monoclonal antibodies to viruses and cells. The monoclonal antibodies against viruses will be used to distinguish and isolate variants of viruses that have different biological activities. The monoclonal antibodies against cells will be used to identify cells with different antigenic determinants and relate these antigens to different biological functions. The Monoclonal Antibody Laboratory is functioning very well and also is beginning to contribute to several of the other ongoing projects in the Laboratory. The second new project involves the use of molecular biological approaches to determine the role of herpes simplex virus (HSV) in the etiology and pathogenesis of tumors of the oral cavity and diseases of the central nervous system. Restriction enzymes are being used to obtain fragments of the HSV genome and these fragments will be cloned and the HSV-DNA will then be hybridized in situ with tumors and cells from the oral cavity and central nervous system. The radioautographs will be examined for the presence of HSV genes in the diseased tissues.

One project has been temporarily dropped because of the loss of Dr. Bennett Jenson from our Laboratory. He was working on hyperplasias and papillomas of the oral cavity (e.g., focal epithelial hyperplasia, oral and laryngeal papillomas). Dr. Jenson developed an immunological technique (peroxidase anti-peroxidase) to rapidly identify oral lesions caused by papilloma viruses. We hope to re-initiate this project as soon as possible to further evaluate the role of human papilloma viruses in a variety of oral lesions, including leukoplakia. Efforts are now being made to recruit a D.D.S. to re-initiate this project and develop a protocol to study the pathogenesis of leukoplakia and the effect of various drugs on the treatment of this disease. The Laboratory's contract on screening for diabetogenic viruses in experimental animals will be terminated this year because of lack of funds.

The staff of the Laboratory continues to work well together on interdisciplinary projects and we are fortunate at this time to have a number of young, talented and aggressive investigators who are doing very nice

work and developing into independently recognized scientists. In addition, Dr. Masakazu Horita, who is a physician from the University of Jikei in Tokyo, just joined our Laboratory as a guest worker. He is studying polyclonal activation and immunoregulatory abnormalities in various autoimmune disorders. Mr. Joel Rosenthal, who was with the Laboratory for almost 13 years left to accept a position in the Extramural Program of NIAID. He was replaced by Dr. Kenneth Cremer, who plans to study the relationship between herpes simplex virus and tumors of the oral cavity and central nervous system. The NIH Visiting Fellow Program continues to supply a steady stream of bright and hard-working investigators from foreign countries who contribute immeasurably to the progress of the Laboratory. The service units of the Laboratory (i.e., tissue culture unit, histology unit, photography unit) and the Office of the Chief continue to function very well.

A number of new techniques have been introduced into the operation of the Laboratory. The principal ones are related to hybridomas and recombinant DNA. Specific methods have been set up for: (1) in vitro protein synthesis; (2) hybridization arrested translation; (3) molecular cloning with cosmids and bacteriophage λ 13; (4) in situ hybridization; (5) selection of enzyme-deficient mutants with drugs; (6) identification of human T cell subsets using monoclonal antibodies; (7) assay of spontaneous polyclonal lymphocyte activation; and (8) a new double fluorescent technique for the identification of specific cell types lysed in a mixed cell population.

Collaboration continues with investigators from many of the other Institutes at NIH, including NIAMDD, NEI, NCI, and NIAID, as well as with colleagues at various universities, including Duke, Walter Reed Army Institute of Research, Mt. Sinai School of Medicine, University of California, University of Tennessee, and Yale.

Some of our more important findings since last year's annual report are summarized below.

1. Herpes simplex virus (HSV) causes a latent infection in trigeminal ganglia of mice and humans. Efforts have continued to determine whether the HSV-DNA is integrated (i.e., covalently linked) into the genome of the host cell. Over the last couple of years, two methods have been used which strongly argue that the latent virus is integrated. Last year, to unequivocally prove that the viral DNA is covalently linked to host cell DNA, efforts were made to clone the joint sequence using recombinant DNA techniques. After screening a half million colonies by hybridization with HSV-DNA, five positive clones were identified. Detailed analysis showed, however, that the cloned sequences were exclusively cellular DNA containing a region of homology with the HSV-DNA. The intriguing and important possibility that these sequences may represent viral integration sites contained in the cellular genome, as in the case with retroviruses, will be explored over the next year.

Progress has been made toward the long-term goal of developing a sub-unit vaccine by use of recombinant DNA techniques. The object is to

clone the segment of the HSV genome coding for the viral glycoprotein (B2) that raises neutralizing antibody. The critical segment of the HSV genome has now been obtained by restriction enzymes and cloned. The gene coding for the major antigenic determinant has been narrowed down to a fragment of viral DNA with a coding capacity of not more than three genes. In the near future, the second phase of the project will be initiated; i.e., insertion of the gene into an expression plasmid capable of producing large amounts of viral proteins in bacteria.

2. Previously, we found that interferon was present in the circulation of patients with certain autoimmune diseases (e.g., systemic lupus erythematosus). Over the last year, we showed that interferon is also present in the circulation of patients with certain types of vasculitis and that the presence of interferon correlates with disease activity. In addition, a patient with a lymphoproliferative disease (T-gamma lymphocytes) was examined in some detail. This study revealed that the patient's lymphocytes spontaneously produced "immune" interferon in vitro, a phenomenon that had not previously been recognized. Since interferon is an "immunoregulatory protein" it is possible that this T-gamma immunoproliferative disease may not be a true malignant proliferation of T cells, but rather a disease caused by disordered immunoregulatory mechanisms. In fact, it is possible that one of the underlying stimuli for proliferation in T cell lymphomas is interferon. Finally, since "immune" interferon is thought to be the most active of the interferons as an immunoregulatory protein, the purification and quantitative recovery of this protein would be invaluable. The finding in this patient of a cell line programmed to produce "immune" interferon may make it possible to "clone" these cells to obtain sufficient quantities of "immune" interferon for both further study and possible treatment of certain immunoregulatory disorders.

3. Monoclonal antibodies now have been obtained that react with Coxsackievirus B4 and EMC virus. Over the next year, these antibodies will be used to reclassify these virus groups and to identify variants of these viruses that have different biological properties.

Recently, we reported that mice infected with reovirus developed autoantibodies that react with their own tissue; pancreas, pituitary, and gastric mucosa. Our present objective is to fuse spleen cells from autoimmune mice with myeloma cells to make hybridomas producing monoclonal autoantibodies. These monoclonal autoantibodies will be used to identify both common and unique autoimmunogens in the animals. This hybridoma technique may also enable us to identify autoantibodies not readily detected in whole sera. In addition, these autoantibodies may serve as useful reagents in the detection and purification of hormones and other biologically important antigens. Thus far, we have succeeded in cloning two strongly reacting autoantibody-producing hybridomas. One of these reacts with pancreas and the other with the anterior pituitary. These autoantibodies will be studied in great detail over the next year. This approach has broad and important applications to a variety of other autoimmune diseases.

4. The surface of cells are known to possess receptors for certain viruses and hormones. The number and nature of these receptors may determine how a cell responds to infection or to the action of a particular hormone.

Using a sensitive radioreceptor assay developed last year, we now have examined the expression and modulation of encephalomyocarditis (EMC) virus receptors on murine lymphoid and myeloid cells. In brief, we found that certain cell types possess receptors and others do not. If, however, receptor-negative cells are stimulated with mitogens, certain of these cells become receptor-positive. Moreover, studies on the binding of virus to receptors during cell growth showed that binding varied by up to 10-fold and was greatest during the exponential growth phase of the cells as compared to the stationary stage. Further studies showed that receptors are present only at certain stages of cell differentiation and that receptors are functionally important in that only cells with a certain number of receptors are susceptible to infection. Thus, this work shows that factors which influence the modulation of viral receptors on the surface of cells may determine the course and outcome of certain viral infections.

For a hormone (e.g., insulin) to exert its biological effect, it must be synthesized, secreted, and transported to target tissues where it must then interact with specific receptors initiating a series of biological events within the cell. Thus, alterations in the number and type of insulin receptors may influence glucose homeostasis. For many many years it has been known that certain bacterial and viral infections can cause a deterioration of carbohydrate homeostasis, and that diabetics often require more exogenous insulin during an infection. The mechanism by which this occurs is not known. Last year we showed that viral infections of cultured human cells resulted in a change in the number of insulin receptors and suggested that viral-induced alterations in the concentration of insulin receptors might be one of the factors leading to abnormalities in glucose metabolism. This last year, experiments were conducted to evaluate the in vivo effect of viral infections on insulin receptors by measuring the binding of ^{125}I -insulin to several different tissues. We found that splenic leukocytes from mice infected with several different viruses showed up to 130% increase in insulin receptors. Moreover, as much as a 300% increase in the binding of ^{125}I -insulin to splenic leukocytes was observed in mice given bacterial lipopolysaccharides. In neither virus-infected nor lipopolysaccharide-treated mice was there any substantial change in insulin receptors in thymocytes, liver membranes or peripheral blood erythrocytes. Thus, the data suggest that during infection, the binding of insulin to peripheral leukocytes, which is widely used to measure insulin receptors, may not accurately reflect the insulin receptor status of other tissues. The experiments also point to the possibility that the increased binding of insulin to receptors on leukocytes might diminish the amount of endogenous or exogenous insulin reaching target organs and be one of the factors responsible for abnormal

carbohydrate metabolism during viral infections. Our studies also point to the possibility that a variety of other mitogenic stimuli may increase insulin receptors on peripheral leukocytes. This may be particularly relevant in patients suffering from immunologically-mediated (e.g., autoimmune) diseases.

5. Diabetes mellitus is a heterogeneous group of diseases. Even the insulin-dependent form appears to have more than one cause; both environmental insults (e.g., viruses) and/or the host immunological response to foreign or self antigens has been implicated. In recent years, autoantibodies have been detected in the sera of many patients with insulin-dependent diabetes mellitus (IDDM). Over the last year, we studied serum from 36 patients with IDDM for their capacity to lyse beta cells. Immunofluorescence revealed an islet cell cytoplasmic antibody (ICA) in 20 patients with IDDM and an islet cell surface antibody (ICSA) in 23 patients. Neither ICA nor ICSA was found in any of the 21 normal controls or 15 patients with noninsulin-dependent diabetes. In the presence of complement, ICSA-positive sera caused significant lysis as measured by the release of ^{51}Cr from cultured rat islet cells, but ICSA-negative serum did not release significant amounts of ^{51}Cr . Proof that ICSA-positive serum was lytic for beta cells was obtained by double fluorescent technique that identified lysed cells by their capacity to take up ethidium bromide and beta cells by their staining with fluorescein conjugated antibody to insulin. These findings suggest that cytotoxic ICSA contributes to the pathogenesis of IDDM, but the mere presence of ICSA does not appear to be sufficient to produce diabetes, since family studies showed that one-fourth of the serum samples from nondiabetic first degree relatives of diabetic probands were ICSA-positive and cytotoxic for beta cells.

What triggers the production of cytotoxic ICSA in patients with insulin-dependent diabetes and their nondiabetic relatives is presently under investigation. There are several possibilities. One is that ICSA is not the cause, but the result of beta cell injury, perhaps secondary to environmental insults (e.g., viruses or chemicals). Another possibility is that ICSA is the host's immune response to foreign antigens that cross-react with surface antigens on beta cells - a form of molecular mimicry. A third possibility is that ICSA precedes the development of diabetes and is the result of an immunoregulatory disorder that is genetically programmed or environmentally induced, or both. Analysis of the long-term effects of ICSA on beta cell function in vivo awaits the results of careful prospective studies. Cytotoxic ICSA may turn out to be a useful predictive marker for identifying persons who are at greater risk of ultimately developing diabetes. Long-term prospective studies are now under way in collaboration with our colleagues at Mt. Sinai Medical School.

EMC virus induces diabetes in certain inbred strains of mice by infecting and destroying pancreatic beta cells; the severity of the diabetes depending on the number of beta cells destroyed. In strains of mice resistant to EMC-induced diabetes, sufficient beta cells are not

damaged to alter glucose homeostasis. However, diabetes can be produced in many species by streptozotocin, a highly specific beta cell toxin. In our experiments, we used concentrations of streptozotocin that did not produce diabetes, but reduced the beta cell reserve. When strains of mice normally resistant to EMC-induced diabetes were first treated with subdiabetogenic doses of streptozotocin then infected with EMC virus, diabetes developed. Furthermore, when mice were infected with viruses such as Coxsackie B3 and B5, which ordinarily produce little if any beta cell damage, diabetes develops if the mice are first treated with subdiabetogenic doses of streptozotocin. These findings suggest that diabetes may result from cumulative beta cell damage induced by sequential environmental insults. These studies, which were carried out over the last couple of years, were reported this year. Moreover, the depletion of beta cells by subdiabetogenic doses of streptozotocin is proving to be a useful model for identifying other diabetogenic viruses, especially those which infect and destroy only a minimum number of beta cells. The enhancement of virus-induced diabetes by low doses of streptozotocin also raises the possibility that in humans a series of viral infections or other environmental insults, each producing some beta cell damage, finally results in overt diabetes once the beta cell reserve has been sufficiently depleted. Further studies on the use of subdiabetogenic doses of streptozotocin to detect beta-tropic viruses are underway and yielding encouraging results.

6. Aphthous stomatitis is a chronic, recurring condition of the oral cavity characterized by single or multiple recurring painful ulcerations which occur in approximately 20% of the population. This last year, two new and important pieces of information about this disease were obtained. First, there appears to be a genetic predisposition in the development of aphthous stomatitis which is associated with certain HLA types. The relative risk of developing aphthous stomatitis in patients who are of HLA types A2 or B12 (Bw44) is 2.9 and 3.0 times greater, respectively, than controls. The nature of the genetic factors remains to be determined. Second, our studies showed that mechanically-induced injury to the oral mucosa can cause ulcerations in individuals prone to develop aphthous stomatitis. The buccal mucosa of 30 patients with recurring aphthous stomatitis and 15 healthy controls were subjected to standardized mechanical injury. One or more ulcers developed in 13 of the 30 aphthous-prone patients, but in none of the controls. These studies point to the possibility that mechanical injury may serve as a method for identifying subsets of patients who are prone to the development of aphthous stomatitis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 DE 00080-08 LOM
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Diseases of the Pancreas and Salivary Glands: Virus-Induced Diabetes		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Notkins, A.L.	Medical Director	LOM NIDR
Yoon, J.W.	Research Microbiologist	LOM NIDR
Dobersen, M.J.	Senior Staff Fellow	LOM NIDR
Aulakh, G.S.	Expert	LOM NIDR
Ray, U.	Visiting Associate	LOM NIDR
Suzuki, H.	Visiting Fellow	LOM NIDR
Onodera, T.	Visiting Fellow	LOM NIDR
McClintock, P.R.	Senior Staff Fellow	LOM NIDR
Kende, M.	Expert	LOM NIDR
COOPERATING UNITS (if any) Dr. Fredda Ginsberg-Felner Mt. Sinai School of Medicine		
LAB/BRANCH Laboratory of Oral Medicine		
SECTION		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland		
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<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords)		
<p>Biological, biochemical and molecular aspects of diabetogenic and nondiabetogenic variants of <u>encephalomyocarditis</u> (EMC) virus are being studied in vitro and in animal model systems. The identification of <u>genetic differences</u> between these variants and molecular mechanisms involved in the <u>pathogenesis of diabetes mellitus</u> are under current investigations. The interaction between various <u>environmental agents</u>, namely viruses and chemicals or among viruses themselves in the pathogenesis of diabetes and long-term complications in animals also has been investigated.</p> <p>The role of the <u>humoral immune system</u> in the <u>pathogenesis of insulin-dependent diabetes mellitus</u> has been studied. This included the identification of <u>auto-antibodies</u> to intracellular components and <u>cell membrane antigens of islet cells</u>. These studies were directed to elucidate the role played by these autoantibodies in the pathogenesis of insulin-dependent diabetes mellitus. Studies to understand the mechanisms involved in <u>virus-induced autoimmunity</u> also are in progress.</p>		

DISEASES OF THE PANCREAS AND SALIVARY GLANDS: Virus-Induced Diabetes

Introduction

In man, there are two major forms of diabetes: insulin-dependent diabetes (IDDM) and noninsulin-dependent diabetes (NIDDM). The pathogenesis and cause of IDDM and NIDDM are thought to differ. Insulin-dependent diabetes generally occurs in a young age group as compared to NIDDM.

The hypothesis that viruses may play a role in IDDM is supported by its abrupt onset, its seasonal incidence, the presence of inflammatory cells in the islets of Langerhans and the destruction of beta cells. In addition, numerous case reports have shown a temporal relationship between the onset of certain viral infections (e.g., mumps, rubella and Coxsackievirus B group) and the subsequent development of diabetes. The recent isolation of a variant of Coxsackievirus B4 from a boy who died shortly after the onset of diabetic symptoms is the strongest evidence to date that lends support to the concept that some cases of IDDM might have a viral etiology. Support for the belief that viruses can trigger some cases of diabetes in man has lately been strengthened by two additional case reports. The first report is that of a 16-month-old child who came down with a Coxsackievirus B5 infection and a few days later developed diabetes. This virus, which was isolated from the feces of the child, produced glucose abnormalities in mice. The second case is that of a 5-year-old girl who developed myocarditis and diabetes 2-3 weeks after open heart surgery. At necropsy, her islets showed a lymphocytic infiltrate and beta cell necrosis. By immunofluorescence, Coxsackievirus B4 antigens were found in the islets and high levels of antibody to Coxsackievirus B4 was found in the serum. In other studies, pancreatic sections from four out of seven neonates who died of Coxsackie B infections showed insulinitis and beta cell damage.

The role of humoral immune mechanisms in the pathogenesis of IDDM also has been intensively investigated. In these investigations, antibodies to intracellular components (islet cell antibodies or ICA) and cell membrane antigens (islet cell surface antibodies or ICSA) have been identified. Studies in our laboratory and elsewhere have helped to define the role of these autoantibodies in the disease process culminating in IDDM. It is likely that ICA appears as a result of islet cell damage since these antibodies are directed against intracellular determinants. Also, ICA is incapable of damaging intact islet cells in the presence of complement. On the other hand, studies described below suggest a more direct role for ICSA in the pathogenesis of IDDM.

In the animal model system, the D and B variants of encephalomyocarditis (EMC) virus are biologically very distinct from each other. The D variant is diabetogenic, whereas the B variant is nondiabetogenic. Immunization of animals with the B variant will protect the animals from

the diabetogenic effects of the D variant. Immunologically, the D and B variants are indistinguishable from each other. There have to be some genetic differences which are responsible for diabetogenic activity of the D variant. We are attempting to elucidate the differences between these two variants of EMC virus by generating radiolabeled probes complementary to EMC virus RNA genome using reverse transcriptase purified from avian myeloblastosis virus and hybridizing these probes with the RNA from these variants. The nucleic acid hybridization studies will reveal the genetic differences or similarities between these two variants within the limits of the sensitivity of this assay.

Objectives

The objectives of these research projects are: (1) to elucidate the role played by viruses and autoimmunity in the pathogenesis of IDDM; (2) to understand the molecular mechanism involved that results in diabetes when animals are infected by the D variant of EMC virus and protected when infected by the B variant; and (3) to use this knowledge to develop ways and means so that IDDM can be controlled in the human population.

Major Findings

Studies in Animal Models: Long-term Complications of Virus-induced Diabetes Mellitus. We have previously shown that the M variant of EMC virus contains two stable variants; one diabetogenic (D variant) and the other nondiabetogenic (B variant). When the D variant was inoculated into SJL/J mice, hyperglycemia developed in over 90% of the animals and they remained diabetic during the observation period of 21 days. In contrast, none of the mice developed diabetes when inoculated with the B variant of EMC virus. To see how long the metabolic changes are maintained in mice infected with the D variant of EMC virus, mice were inoculated with the virus and at different times thereafter, nonfasting blood glucose levels were determined. The mean blood glucose level of 100 mice was 430 mg/dl at 7 days after infection and 85% of the animals were hyperglycemic. The severity of the hyperglycemia and the percentages of diabetic animals, however, continuously decreased. At 30 days after infection, the mean nonfasting glucose was about 400 mg/dl and 78% of the animals were hyperglycemic. At the end of six months, the mean blood glucose level was 257 mg/dl and only 16% of the surviving animals had elevated glucose levels. In contrast, age-matched uninfected control mice showed no elevation of blood glucose. To see the relationship between virus-induced hyperglycemia and immunoreactive insulin (IRI), mice were infected with the D variant of EMC virus and at different times thereafter, the concentration of IRI in plasma and blood glucose levels was determined. Up to 150 days after infection, the animals could be segregated into two groups: one with normal plasma IRI and normal glucose levels, and the other with depressed plasma IRI and elevated glucose levels. However, at 180 days after infection, plasma IRI somehow elevated and glucose levels decreased. This could be due to the significantly

increased mortality of severely diabetic mice. The remaining animals had relatively mild diabetes, probably secondary to the regeneration of beta cells in the pancreas. To see whether diabetic animals would show higher mortality than nondiabetic animals, the mortality of virus-induced diabetic animals and nondiabetic animals was determined. The mortality of diabetic mice was significantly higher than that of uninfected animals or infected nondiabetic animals.

To see whether renal and ocular complications occur, mice with prolonged diabetes were examined for histopathologic changes. About one-third of the diabetic mice showed mild glomerular changes after four months of persistent hyperglycemia and approximately two-thirds of the animals showed moderate renal alterations. Furthermore, most animals showed severe structural changes in the kidneys after six months of persistent hyperglycemia. Light microscopy of the kidneys of mice with diabetes for six months showed thickened Bowman's capsule, nodular and diffuse glomerulosclerosis, increased mesangial matrix and thickened tubular and peripheral glomerular basement membranes. The afferent and efferent arterioles showed evidence of hyaline sclerosis. In age-matched controls, the glomeruli, tubules, and arterioles appeared normal. Transmission electron microscopy revealed moderate thickening of the peripheral glomerular basement up to two to three times the normal thickness. The foot processes were fused in some areas and intact in others. The mesangium was markedly thickened. Scanning electron microscopy of the glomerulus revealed focal effacement of the surface contour and considerable atrophy of some glomeruli, some of which occupied only a third to one-half of Bowman's capsule. In addition to renal complications, ocular abnormalities were observed in the cornea and retina of some animals. The corneal epithelium showed marked irregularity of cell layers, particularly of the basal layer. Trypsin digest preparation of retinal vessels revealed decreased numbers of pericytes in diabetic mice. Retinal capillaries showed minimal to moderate thickening of basement membrane. In conclusion, renal and ocular complications observed in prolonged diabetic mice were similar to those seen in humans with diabetes mellitus.

Molecular Studies - RNA. A radiolabeled probe complementary to the D variant of EMC viral RNA hybridized equally well to homologous and heterologous RNAs. The reciprocal hybridization experiments using a ^{32}P -labeled cDNA probe of the B variant confirmed these findings. There are no detectable differences between D and B variants of EMC virus. Differences in the genomic makeup of these two variants are too small to be identified by total nucleic acid hybridization technique. The genomic structure seems to be very similar. Thermal melting experiments of hybrids show identical profiles, indicating very little, if any, mismatching of the nucleotides. The hybrids with ^{32}P -labeled cDNA probe of the B variant RNA gave a different thermal elution profile than the hybrids with ^3H -labeled cDNA probe of the D clone. The lower t_{e50} transcripts were missing in the ^{32}P -labeled cDNA probe of B clone. It may be due to the fact that the B clone RNA was treated with methylmercury

hydroxide to relax the RNA molecule by removing the secondary structures. It will be interesting to see if methylmercury hydroxide treatment produces similar results with the transcript of D clone RNA. It seems that there is a strong secondary structure very close to the 3' end of the RNA molecule which serves as a strong stop during the cDNA synthesis. The hybrids with ^{32}P -labeled cDNA probe of B RNA gave 6-7° higher t_{e50} than the hybrids with ^3H -labeled cDNA probe. The t_{e50} is influenced by GC content and size of the hybrids. Attempts will be made to determine which of these factors is contributing to the high t_{e50} .

Experiments are in progress to clone the complete genome of D and B variants using recombinant DNA technology. There are some problems in getting a complete transcript of the viral RNA genome, however, efforts are being made to get this genome and clone it.

The RNAs of B and D variants have been sized by using methylmercury denaturing gels and AMV RNA as a marker, which is 7500 nucleotides long. The D and B clone RNAs are slightly bigger than AMV RNA, approximately 7700 nucleotides long, and of the same size when compared with each other.

Molecular Studies - Proteins and Fingerprinting. Studies of the physical and physiological properties indicate that the two variants have identical properties. The coat proteins and RNA are of the same sizes, although the B-RNA seems to be more unstable than D-RNA. The four-coat proteins have identical electrophoretic mobility on gel. The individual coat proteins, at present, are being analyzed by tryptic fingerprinting and V8-enzyme digestion. The individual proteins are also being sequenced for amino acid composition. These studies should reveal any small difference in coat proteins between the two variants.

Our initial studies with RNAs of the two variants yielded some interesting results. We performed oligonucleotide fingerprinting after T1-digestion of the RNAs from these viruses. On repeated attempts, the fingerprints always exhibited a difference in one particular spot between the two variants. An oligonucleotide of about 20-25 bases long was found to be missing from the B-RNA fingerprint, but was present in the D-RNA fingerprint. We do not, as yet, know from what part of the genome this oligonucleotide is missing. If it happens to be missing from the regulatory part of the genome, then fingerprinting or sequence analysis of the coat proteins would not show any difference. Sequencing of the complete RNA genome only (or cDNA) would be the logical experiment to obtain more information about these viruses.

Coxsackieviruses. Diabetogenic variants of Coxsackievirus B1, B2, B3, B5 and B6 have been studied in vivo in the animal model system. Coxsackieviruses originally obtained from the American Type Culture Collection have been passaged in cultures enriched for pancreatic beta cells to produce variants that induce a diabetes-like syndrome in SJL/J mice.

Beta cell passaged virus induced various degrees of abnormality in glucose tolerance tests (e.g., 60% for Coxsackie B1, 50% for Coxsackie B2, 36% for Coxsackie B3, 50% for Coxsackie B4, 32% for Coxsackie B5, and 5% for Coxsackie B6). Histopathology from animals infected with beta cell passaged Coxsackievirus revealed various degrees of destruction of beta cells and infiltration of mononuclear cells in the islets. Frozen sections from the pancreas of infected mice also were stained with FITC-labeled antibodies to Coxsackieviruses. Coxsackie B1, B3 and B5 infected mice showed viral antigens in the islets at 4 days after infection, but not in acinar cells. In comparison, Coxsackie B2 and B6 infected mice showed less viral antigens in their islets.

To confirm these observations, we used a double-antibody technique with FITC-labeled anti-Coxsackievirus antibody and TRITC-labeled anti-insulin antibody. Frozen sections of pancreas from animals infected with Coxsackie B5 were stained with both antibodies simultaneously. When fluorescein filters were used, cells containing viral antigen appeared green. When the same sections were examined with rhodamine filters, insulin-containing B cells in the islets of Langerhans appeared orange. By double-exposure photography, insulin-containing B cells infected with Coxsackievirus were readily identified by their orange-green or yellow color.

Further proof that Coxsackieviruses replicate in B cells comes from treatment with sub-diabetogenic doses of streptozotocin before virus infection. Preliminary experiments showed that by reducing the B cell reserve with a sub-diabetogenic dose of streptozotocin, it was possible to produce diabetes in strains of mice which were usually resistant to Coxsackie virus-induced diabetes. Our experiments showed that streptozotocin enhanced the virus-induced diabetes of the animals by 40 to 60% in B1, B2 or B6 infected mice and by 20 to 30% in B3 or B4 infected mice.

From these studies, it appears that the various subtypes of Coxsackieviruses differ in their ability to cause diabetes under similar conditions in an animal model system. By plaque isolation technique, it should be possible to clone more diabetogenic viruses and to compare the difference between diabetogenic and nondiabetogenic clones.

Reovirus and Autoimmunity. The cause of insulinitis is not known, but it has been suggested that viral infections and/or immunologic mechanisms may play a role in the etiology and pathogenesis of IDDM. IDDM is sometimes associated with autoantibody to pancreatic islets and some other hormone-producing cells (e.g., thyroid, gastric mucosa, adrenals, pituitary). What triggers the production of these autoantibodies is not known, but viral infections have often been suspected as a cause of autoimmune disease. The present investigation was initiated to see whether viruses that produce diabetes in animals also would trigger an autoimmune response.

Earlier studies from our laboratory showed that reovirus type 3, which is widely disseminated in the human population, could infect pancreatic beta cells in mice and produce diabetes. This year, we showed that reovirus type 1 also produces diabetes in mice, but in addition, causes polyendocrinopathy and triggers the production of autoantibodies to insulin and growth hormone (GH).

Mice infected with reovirus type 1 developed transient diabetes and a runting syndrome. The diabetes was characterized by hyperglycemia. Inflammatory cells and viral antigens were found in the islets of Langerhans and virus particles were seen in beta, alpha and delta cells. The runting syndrome consisted of retarded growth, oily hair, alopecia and steatorrhea. Inflammatory cells and viral antigens were found in the anterior, but not posterior pituitary. Electron microscopy revealed virus particles in growth hormone (GH)-producing cells and by radioimmunoassay the concentration of GH in the blood was found to be decreased.

Examination of sera from runted mice revealed the presence of autoantibodies which by immunofluorescence reacted with cytoplasmic antigens in the islets of Langerhans, anterior pituitary and gastric mucosa of uninfected mice. Absorption studies and enzyme-linked immunosorbent assays designed to identify the involved antigens showed that some of the autoantibodies were directed against insulin and GH.

In contrast, preliminary studies in our laboratory showed that reovirus type 3 failed to induce autoantibodies to GH. To see if a specific segment of the viral genome was required for the induction of autoantibodies, recombinants between reovirus type 1 and type 3 were used. When mice were infected with recombinant 3.HA1 (i.e., nine genes from reovirus type 3 and the S1 gene and hemagglutinin from reovirus type 1), all the mice developed antibodies to GH. In contrast, when mice were infected with recombinant 1.HA3 (i.e., nine genes from reovirus type 1 and the S1 gene and hemagglutinin from reovirus type 3), none of the mice developed autoantibodies to GH. Similarly, mice infected with clone 94 (i.e., a recombinant containing five genes from type 1 and five genes, including S1, from reovirus type 3), did not develop autoantibodies to GH. These experiments show that the S1 gene from reovirus type 1 is required for the induction of autoantibodies to GH.

Immunological Studies. In the past year, we have expanded our studies on islet cell surface antibody (ICSA). Previously, we found that, in the presence of complement, ICSA-containing serum was lytic for newborn rat beta cells. This was determined by a novel double-fluorescence technique in which lysed cells were identified simultaneously by their uptake of ethidium bromide into the nucleus (appearing orange) and as beta cells by their staining with fluorescein-labeled insulin antibody (appearing green). Recently, we have modified this technique using antibodies to the other islet hormones (glucagon, somatostatin and pancreatic polypeptide) to determine whether ICSA also was capable of lysing alpha, delta and PP cells.

Twelve ICSA-containing sera and ten normal controls were tested in this way. The mean percentage (\pm SD, $n = 12$) of each cell type lysed by ICSA was as follows: beta cells, 81 ± 7.2 ; alpha cells, 9.6 ± 2.8 ; delta cells, 4.0 ± 1.5 ; and PP cells, 7.0 ± 2.7 . Control sera typically resulted in lysis of $<5\%$ of each islet cell type. In summary, ICSA causes significant lysis of only beta cells and not the other cell types.

The demonstration that ICSA is preferentially lytic for beta cells may be important in defining the role of these autoantibodies in the pathogenesis of IDDM, particularly since histopathologic studies indicate that the beta cell mass is markedly reduced relative to the other cell types. Quantitative morphometric analyses of islets from insulin-dependent diabetics show that non-beta islet cells are actually present in increased numbers. Also, the specificity of ICSA suggests its potential application in the purification of beta cells by flow cytometry or various affinity techniques.

We are currently using ICSA-containing serum to isolate and eventually purify the corresponding beta cell associated antigen. Successful completion of this study will allow further work on the biochemical characterization and immunological properties of this antigen. In addition, islet cell antigen purified in this way would be essential in developing and standardizing a sensitive radio- or ELISA-type assay for ICSA.

Also, during the past year we have developed an improved microcytotoxicity assay for ICSA. Comparative studies showed that both primary rat islet cells and insulinoma cells were lysed to a large extent by ICSA+ serum in the presence of complement. Furthermore, only primary rat islet cells and insulinoma cells were able to remove almost entirely the cytolytic activity of the serum, indicating that they share common cell surface antigenic determinants. These antigens serve as target antigens in the cytolysis. Additionally, only the insulin-producing cells, but not the normal rat fibroblasts, normal epithelial and rat fibrosarcoma cells were lysed with serum from IDDM patients. Since insulinoma cells could be used as effectively as primary rat islet cells to detect cytotoxic antibodies, the former were used as target cells in the determination of the prevalence, duration and titer of cytotoxic antibodies in 159 IDDM patients. At the time of diagnosis, 60% (21/35) of sera from patients with IDDM had cytotoxic antibodies. The frequency of these antibodies progressively decreased with the duration of the diabetes and after 37 months, only 23% of the patients had cytotoxic antibodies in their sera. In a few patients, low levels of autoantibodies were detected between 5 and 10 years after diagnosis. Only 6% (2/23) of patients with noninsulin-dependent diabetes and none of the normal controls (0/38) had cytotoxic activity in their sera. Since the insulinoma cell line is homogenous, there is no question as to cell types lysed with the serum of IDDM patients. The presence of cytotoxic antibodies in a large

portion of IDDM patients suggests that these antibodies might participate in the pathogenesis of IDDM.

Screening for Diabetogenic Viruses. In 1979, a contract was awarded to Microbiological Associates for the purpose of screening viruses suspected of being able to infect pancreatic beta cells and induce a diabetes-like syndrome. Screening was done by inoculating the viruses into neonatal or adult mice and rats. Each virus was given a first screen in which plasma glucose levels and the extent of virus replication in the islets of Langerhans were measured by immunofluorescent staining. In some cases, a more detailed second screening was used in which plasma glucose and insulin and pancreatic insulin were measured, and pancreatic tissues were prepared for light and electromicroscopic evaluation.

Murine cytomegalovirus (CMV), a herpesvirus, was tested in several screens. This virus is analogous to the human cytomegalovirus for which evidence of beta cell infection and induction of diabetes has been found. As with other herpes viruses, murine and human CMV can become latent in infected tissues and may reactivate to a productive infection at a later time, usually following an immunosuppressive stimulus. Therefore, murine CMV was screened in neonatal and adult mice in a primary infection, as well as by reactivating the virus with immunosuppressive agents in mice previously infected as neonates. Primary infection of neonates and adults yielded no evidence of a diabetogenic effect, nor was any change in glucose homeostasis observed in animals latently infected with CMV and subsequently infected with the immunosuppressive BALB/c leukemia virus to reactivate the CMV infection. However, a first screen involving reactivation of latent CMV by cyclophosphamide (an immunosuppressive drug) did yield somewhat equivocal evidence of beta cell damage. A second screen, using cyclophosphamide-induced reactivation was done and showed transient but significant elevations in plasma glucose and depressions in plasma insulin relative to uninfected cyclophosphamide-treated animals at days 5 and 7 following reactivation. These experiments will be repeated.

Last year, we reported that neither EMC virus nor mumps virus was found to be diabetogenic in F344 rats. Because other laboratories have reported that mumps virus-infected Wistar rats become glucose intolerant, the contractor was given additional rat beta cell passaged mumps virus to be screened in three strains of rat: Wistar Furth, Buffalo, and F344. No diabetogenic activity was observed in any of the strains. Even when pretreated with a sub-diabetogenic dose of the drug streptozotocin, rats challenged with mumps virus remained normoglycemic. Exactly the same results were obtained using rat beta cell passaged Coxsackievirus B4 and three variants of EMC virus. For reasons that are not known, rat beta cells appear to be highly resistant to these viruses in vivo, although in vitro these viruses infect and destroy cultured rat beta cells.

In 1980, it was reported that ten clones of EMC virus were screened, and that the results showed that some clones were highly diabetogenic

while others induced little or no diabetes. Three of the clones were re-examined to confirm the original observation and to obtain more information on the types of diseases induced in mice. Of the three clones, one had been found to be highly diabetogenic, one induced no observable disease, and one induced a fatal disease. Upon rescreening using high and low doses of virus by the intraperitoneal, intravenous, and oral routes of infection, the previous results were corroborated. Although this study is still in progress, preliminary results suggest that the diabetogenic clones are highly beta cell tropic, whereas the clone found earlier to induce a lethal disease apparently has a strong tropism for the myocardium. The tropisms are the same regardless of the route of inoculation. Along with the other EMC variants previously isolated in the LOM, a detailed analysis of these clones may permit identification of the characteristics which render a given virus diabetogenic or nondiabetogenic.

Summary and Future Studies

Long-term complications (renal and ocular) of diabetes mellitus induced by the D variant of EMC virus were similar to those seen in humans with diabetes mellitus. Mice infected with Coxsackievirus B1, B2, B3, B4, and B5, when serially passaged in pancreatic beta cell cultures, developed abnormal glucose tolerance tests. Reovirus type 1, which produces diabetes in mice, causes polyendocrinopathy and triggers the production of autoantibodies to insulin and growth hormone.

Nucleic acid hybridization studies reveal that the RNA genome of the D and B variants of EMC virus are very similar. The t_{e50} studies of homologous and heterologous hybrids indicate very little if any mismatching. Oligonucleotide fingerprints show the absence of a 20-25 base long segment in the RNA of B clone which is present in the RNA of the D clone. The purified individual coat proteins are being studied by tryptic fingerprinting to evaluate small differences between the two variants.

Work on the immunological aspects of IDDM has progressed in the characterization of ICSA and methods used for its identification. The demonstration that ICSA is specifically lytic for beta cells has formed the basis for further efforts in the characterization of beta cell surface determinants and their role in the autoimmune process.

Our future plans for research are aimed at (1) isolating virus from patients with acute IDDM and determining if these viruses are diabetogenic in the animal model system, (2) establishing the role of viruses in triggering autoimmune pathology, and (3) determining the role of autoantibodies in the induction of diabetes.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00094-08 LOM
PERIOD COVERED <p style="text-align: center;">October 1, 1980 - September 30, 1981</p>		
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">Ulcerative Lesions and Tumors : Recurrent Aphthous Stomatitis</p>		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Wray, D. Oppenheim, J.J. Strober, W. Notkins, A.L.	Visiting Associate Medical Director Medical Director Medical Director	LOM NIDR LMI NIDR MET NCI LOM NIDR
COOPERATING UNITS (if any)		
LAB/BRANCH <p style="text-align: center;">Laboratory of Oral Medicine</p>		
SECTION		
INSTITUTE AND LOCATION <p style="text-align: center;">NIDR, NIH, Bethesda, Maryland</p>		
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<input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <p> The purpose of this project is to investigate the <u>pathogenesis</u> of <u>recurrent aphthous stomatitis</u> and to develop effective <u>therapy</u>. <u>Immunological studies</u> include <u>HLA typing</u>, which has shown an association with HLA types <u>A2</u> and <u>BW44</u>, <u>lymphocyte transformation</u>, which is depressed, and assays for <u>cytokines</u> and <u>macrophage suppression</u> which are normal. Other studies are underway to examine <u>polymorph function</u> and <u>T helper</u> and <u>T suppressor</u> cell function as well as <u>immunoglobulin</u> production measured by <u>Elisa</u>. </p> <p> Clinical studies include gathering <u>epidemiological</u> data on patients and <u>hema- tological</u> studies. <u>Food allergy</u> and <u>trauma</u> have been identified as <u>initiating factors</u> and the assessment of various drugs on a <u>double-blind</u> basis including <u>zinc sulphate</u> and <u>cimetidine</u> are underway. </p>		

RECURRENT APHTHOUS STOMATITIS

Background and Objectives

Recurrent aphthous stomatitis is a chronic recurring condition of the oral cavity characterized by single or multiple recurrent painful ulcerations which occur in approximately 20% of the population. In the past, these ulcerations have been thought to be autoimmune in nature. Recent studies have indicated that it is possible to modulate or eliminate some aphthous ulcers by replacing deficiencies of iron, folic acid or vitamin B12. In addition, some cases of recurrent aphthous stomatitis are associated with an increased incidence of celiac disease (gluten-induced) enteropathy.

The purpose of this project is to study the pathogenesis of recurrent aphthous stomatitis with the ultimate aim of treating and preventing this condition.

Streptococcus sanguis can be isolated from recurrent aphthous lesions. It is the purpose of this study specifically to investigate patient's immune response against this organism when compared with a normal control population without ulceration and to identify methods of modulating any deviations from normal in the immune response seen in these patients.

Preliminary data suggest the immune response to streptococcus sanguis is inappropriate using lymphocyte proliferation as an index. It is the intention, therefore, to further characterize this immune response by investigating several aspects. Lymphocyte proliferation has been assessed as has the role of macrophages in this response. At present, T suppressor cell assays are underway as well as identification of subpopulations of lymphocytes. Immunoglobulin production in these patients is being measured in serum and saliva, both for total class-specific immunoglobulin and antistreptococcus sanguis antibodies, using an ELISA assay. In addition, because of the familial tendency in this disease, patients and families have been HLA typed. Polymorphonuclear leukocytes predominate in established lesions and, hence, assessment of peripheral blood and lesional polymorphological function is being carried out. Recent evidence suggests that K cell activity is increased in aphthae patients and, hence, ADCC assays are being performed.

A number of environmental factors appear important in initiating the disease process, therefore, several clinical studies have been undertaken to assess the relative importance of trauma, stress, food allergy, hormonal influences, hematological deficiencies, malabsorption, and other associated gastrointestinal diseases. In addition, careful epidemiological data is being collected to more clearly define the natural history of the disease. Furthermore, a number of clinical trials are being conducted to assess the value of empirical therapy and to test the efficacy of drugs chosen after consideration of what is known about the pathogenesis.

Major Findings and Implications

To date, it has been demonstrated that patients' lymphocytes have a higher rate of spontaneous proliferation and that they have a significant hyporesponsiveness to streptococcus sanguis. Cytokine production, however, is unaltered. Specifically, chemotactic factor, lymphocyte activating factor (Interleukin I) and T cell growth factor (Interleukin II) are produced normally. Macrophages have been shown not to be responsible for the hypo-responsiveness seen.

Patients show an inability to generate concanavalin A-induced suppression due to their hyporesponsiveness which strengthens the hypothesis that a T suppressor cell is involved. Assays for T suppressor cells have begun which indicate that patients with aphthae produce less in vitro immunoglobulin than controls. Further analysis of this phenomenon is underway.

HLA typing was carried out on 49 unrelated patients with recurrent aphthous stomatitis. In addition, a total of 100 individuals were typed from 14 families of these patients in order to establish the HLA phenotypes in families where more than one member of the family was affected. Analysis of family inheritance patterns in 100 families including those who were HLA typed was unhelpful in establishing the genetics of this disease. In the 49 unrelated individuals typed, however, the HLA types A2 and B12 (Bw44) showed a significant correlation with disease (relative risk 2.9 and 3.0, respectively). It is felt that susceptibility is determined genetically and that disease expression is influenced by environmental factors.

The buccal mucosa of 30 patients with recurrent aphthous stomatitis and 15 healthy controls were subjected to standardized mucosal injury. This was achieved by establishing local anesthesia (two needle puncture wounds) and then inserting a towel tenaculum briefly into the buccal mucosa (two wounds) and, finally, inserting a suture for 24 hours (two wounds). Lesions developed in 13 patients (26 ulcers from a total of 180 injury sites) and none in controls ($p < 0.001$). The sutures caused the most lesions and the needle wounds the least. Mechanically-induced lesions were indistinguishable clinically and histologically from spontaneous lesions. These findings are similar to the response to skin injection seen in patients with Behcet's syndrome who develop skin pustules after injections. This exaggerated response to mucosal injury may be due to defective wound healing or the effects of inflammatory mechanisms such as histamine.

The leukocytes from 60 patients with recurrent aphthous stomatitis were tested for histamine release in response to environmental and food antigens. Eighteen patients (30% of the population studied) were atopic and this history of respiratory allergy was confirmed by an in vitro histamine release assay. The non-atopic patients with recurrent aphthous

stomatitis had a significantly higher incidence of in vitro histamine release to foods than controls. The leukocytes from 23 patients (38%) released histamine to food antigens. Patients eliminated foodstuffs in a double-blind trial to correlate the in vitro histamine release to the development of oral ulcers. Only 30% of the patients had a decreased incidence of ulcers after eliminating foods which had induced in vitro histamine release. On rechallenge in the double-blind trial, 30% of the foods which caused histamine release also correlated to increased incidence of oral lesions. In eight patients, ingestion of certain foodstuffs were correlated to oral ulceration by food diaries and elimination-rechallenge in an open-trial basis. However, dietary manipulation did not completely eliminate the ulceration in any of the patients. The results suggest that food sensitivity may play a minor role in the development of recurrent aphthous stomatitis.

A double-blind crossover trial on the effects of systemic zinc sulphate was carried out on 25 patients with recurrent aphthous stomatitis. No therapeutic effect was seen with the use of systemic zinc over a three-month period. This study fails to confirm the beneficial effects seen with zinc in previously reported studies. Four patients had to discontinue the zinc therapy because of side effects. The empirical use of systemic zinc sulphate supplementation in the treatment of recurrent aphthous stomatitis is not recommended.

Significance to Biomedical Research

The observation that trauma and food allergy can induce ulceration, probably by histamine release, strengthens the view that a T suppressor cell is involved which is activated by histamine. To test this hypothesis, a double-blind trial of the H2 antagonist, cimetidine, is being carried out. It is felt that an isotype-specific IgA suppressor may allow intra-epithelial deposition of IgG or IgM, which could then encourage ADCC-type killing of the target tissue. Isotype-specific T suppressor cell assays and ADCC assays are, therefore, being carried out. In addition, the role of polymorphonuclear function in the pathogenesis is being researched by using functional assays for peripheral blood and intra-lesional leukocytes.

Proposed Course

If the concept of isotype-specific T cell suppression can be established, this has broad implications for other mucosal diseases, both oral and gastrointestinal.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 DE 00123-08 LOM																
PERIOD COVERED October 1, 1980 - September 30, 1981																		
TITLE OF PROJECT (80 characters or less) Herpes Simplex Virus: Latency																		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 40%;">Puga-Carrasco, A.</td> <td style="width: 30%;">Senior Staff Fellow</td> <td style="width: 10%;">LOM</td> <td style="width: 20%;">NIDR</td> </tr> <tr> <td>Cantin, E.M.</td> <td>Expert</td> <td>LOM</td> <td>NIDR</td> </tr> <tr> <td>Cremer, K.J.</td> <td>Senior Staff Fellow</td> <td>LOM</td> <td>NIDR</td> </tr> <tr> <td>Notkins, A.L.</td> <td>Medical Director</td> <td>LOM</td> <td>NIDR</td> </tr> </table>			Puga-Carrasco, A.	Senior Staff Fellow	LOM	NIDR	Cantin, E.M.	Expert	LOM	NIDR	Cremer, K.J.	Senior Staff Fellow	LOM	NIDR	Notkins, A.L.	Medical Director	LOM	NIDR
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SUMMARY OF WORK (200 words or less - underline keywords) The aim of this project is to study the <u>latency</u> of <u>herpes simplex virus (HSV)</u> in the <u>peripheral nervous system</u> and <u>central nervous system</u> and to develop a coherent approach to <u>diagnosis</u> and <u>prevention</u> based on <u>molecular biological studies</u> . The <u>physical state</u> of the <u>latent viral genome</u> is being determined by <u>DNA-hybridization</u> techniques and <u>molecular cloning</u> .																		

HERPES SIMPLEX VIRUS: Latency

Animal Model and Molecular Biology. Recurrent disease is the clinical hallmark of herpes simplex virus (HSV) infection. After primary infection, which occurs in childhood, the virus remains latent for years in sensory and autonomic ganglia of the nervous system. At irregular intervals, HSV is reactivated in ganglia and causes epithelial lesions. Estimates of yearly reactivations or recurrences include 98,000,000 episodes of herpes labialis, 2,000,000 episodes of genital herpes, and a half million episodes of corneal herpes. Furthermore, genital infections with HSV type 2 are fast acquiring epidemic proportions that makes it one of the major causes of venereal disease, not only in the U. S., but all over the world. In addition to this considerable morbidity, fatal infections occur both in newborns with a generalized infection and in adults with sporadic encephalitis.

In the past, the primary interest of this laboratory has been the pathogenesis of the recurrent HSV disease, and our efforts have been directed to prevention of the ganglionic infection by immunization and antiviral therapy. All of our work has been done using BALB/cJ mice as a laboratory model. The development of a rational therapy to prevent reactivation demanded a fuller understanding of viral latency at the molecular and immunological levels.

At the molecular level, a central question is the physical state of the viral genome. At the immunological level, it is crucial to determine what role immunological factors play in establishing and maintaining the latent state.

About a year ago, the potential of recombinant DNA technology was recognized as a means to develop a subunit vaccine against HSV. One of the major antigenic determinants of the virus, the B2 (gB) glycoprotein, was chosen for its production in *E. coli* bacteria. The effectiveness of such approach to antiviral therapy would eventually be evaluated in our animal model system.

Finally, with the demonstration from our laboratory of the presence of viral DNA sequences in brains of latently infected mice, it becomes paramount to determine the role, if any, of HSV in neurological disease in humans. Enough knowledge has been accrued during the past few years about the molecular biology of the infection in the animal model to allow posing pertinent questions in human disease.

This progress report will address the major areas outlined above, viz.: (1) studies of the physical state of the viral genome during latency, (2) identification of the B2 gene by recombinant DNA techniques, (3) immunological studies and reactivation, and (4) HSV sequences in normal and diseased tissues from humans.

Physical State of the Viral Genome. Experiments begun last year to determine the physical state of the latent viral genome in trigeminal ganglia of mice were continued and expanded during the current year.

The experimental strategy outlined in last year's report was to determine whether the termini of the viral genome, as defined by the restriction endonuclease EcoRI, were covalently joined to cell DNA sequences. DNA was extracted from the trigeminal ganglia of 400 latently infected mice. It was estimated by molecular hybridization in the liquid phase that 0.003% of the total DNA content was viral. In terms of total mass, this percentage corresponded to approximately 20 ng of viral DNA in a total of 6 mg of trigeminal ganglion DNA recovered. Since the viral termini amount to 4% of the viral genome, the relative abundance of these fragments would be approximately $1.2 \times 10^{-4}\%$, or close to 1 ng per 6 mg. Scarcity of DNA was then an important factor in the design of our experimental approach, since it precluded the use of techniques that require a large number of assays.

The DNA obtained was digested to completion with EcoRI and the restriction fragments separated on the basis of size by preparative gel electrophoresis on 0.6% agarose gels using the apparatus built in the NIDR machine shop. The DNA sizes ranged uniformly from a few bases up to 25-30 kilobase pairs (kb). An aliquot of each fraction was probed for the presence of one of the viral DNA termini, the EcoRI K fragment, using liquid DNA-DNA hybridization to a ^{32}P -labeled K DNA cloned in the bacterial plasmid PBR 322. The results from this experiment indicated that 83% of the K-like sequences in ganglia were present in DNA species ranging in size from 6.7 to 12 kb. Since the viral-derived K DNA fragment has a size of 5.7 kb, it was concluded that 83% of the viral terminus had a piece of cell DNA joined to it ranging in size from 1.0 to 6.3 kb. In addition, 9% of the K-like sequences were found in the range of 4.2-6 kb, where the viral K DNA was expected, and the remaining 8% was found in sizes below 4.2 kb.

Fractions containing K DNA sequences were then digested with the restriction enzyme Bam H-I and electrophoresed in 0.9% agarose gels. Bam HI cleaves the K fragment once, yielding a terminal 3-8 kb fragment and an internal fragment of 1.9 kb. The gel was blotted onto nitro-cellulose paper by the method of Southern and hybridized to a ^{32}P -labeled cloned K DNA probe. The result from this experiment showed the presence of the terminal fragment at various discrete bands, ranging in size from 4.0 to 9.0 kb.

These results agreed qualitatively with those obtained during the past year using a different technical approach, viz. RPC-5 chromatography. After consultation with several colleagues, it was decided that in order to prove unambiguously covalent joining of cell and viral DNA sequences, it would be necessary to clone these joined sequences using recombinant DNA techniques. To this effect, we sought and obtained approval from the NIH Biosafety Committee.

The strategy employed was as follows. Since the viral K fragment contains no Hind III restriction site, digestion of the putative joint sequences with Hind III would result in DNA pieces having either EcoRI-EcoRI ends or EcoRI-Hind III ends; in the second case, the EcoRI site would always be in the HSV portion and the Hind III site in the cellular portion of the fragment. These sequences could then be cloned in a vector containing EcoRI-Hind III cloning sites. Fragments containing EcoRI-EcoRI ends would not clone in such vector, resulting in the loss of any joint sequences that do not contain Hind III sites. However, since this approach would lower by several orders of magnitude the background of relegated vector molecules, it was chosen for a preliminary experiment.

EcoRI cleaved, trigeminal ganglion DNA from the appropriate fractions was digested with Hind III and DNA species higher than 6.0 kb were purified in sucrose gradients, ligated to the EcoRI-Hind III arms of the Lambda Charon 27 bacteriophage using T4 DNA ligase and packaged into phage heads in vitro. A total of 5×10^5 pfu was obtained. The probability of finding at least one clone containing K sequences was determined by the equation of Carbon at 11%. Although this probability was low, all 5×10^5 pfu's were screened using plaque lifts onto nitrocellulose paper and hybridization to our cloned K probe. Five positive recombinants were found. However, none of the five proved to contain the totality of the K-DNA sequences. On finer mapping, they were shown to comprise exclusively cellular DNA sequences containing a region of homology with the viral DNA. This region is probably short, of not more than 100 bp, and hybridizes somewhere in the terminal-most 2.8 kb of the viral genome. These sequences may represent viral integration sites contained in the cellular genome, as is the case with retroviruses. This intriguing possibility will be explored in the future, using finer mapping with restriction enzymes and/or DNA sequencing techniques.

We are at present cloning again the viral sequences from latently infected trigeminal ganglia. In order to maximize the probability of obtaining the desired clone(s), the experimental design has been scaled up by two orders of magnitude. Forty micrograms of selected DNA molecules containing EcoRI-EcoRI ends, EcoRI-Hind III ends, and Hind III-Hind III will be ligated to the appropriate cloning sites in 460 μ g of the Lambda Charon 30 phage DNA. A high efficiency packaging extract has been made that would yield approximately 5×10^7 - 1×10^8 total pfu's. Under these conditions, the probability of finding at least one desired clone is greater than 95%. The library will be size fractionated in CsCl gradients and amplified prior to screening.

A primary screening will be done in bulk, by cleaving an aliquot of the amplified phage with EcoRI and Hind III and electrophoresing the DNA fragments in agarose gels. The gels will be transferred onto nitrocellulose sheets bi-directionally, which will produce two identical replicas of each gel. One sheet will be hybridized to total HSV DNA and

the other to a cloned K probe that does not contain the terminal 2.8 kb. In this manner we expect first, to detect all of the viral fragments in trigeminal ganglia, and second, to detect bonafide integration by ruling out the cellular sequences that hybridize to the terminal-most viral 2.8 kb.

Identification of the B2 Gene by Recombinant DNA Techniques. In 1980, we embarked on a collaborative interinstitutional project to produce a safe effective HSV1 sub-unit vaccine using recombinant DNA technology (Annual Report 1980).

Initial studies in the LOM were directed towards cloning an HSV1 restriction endonuclease fragment (XbaI-F) containing the B2 (gB) glycoprotein gene, which is one of the major antigenic determinants of this virus.

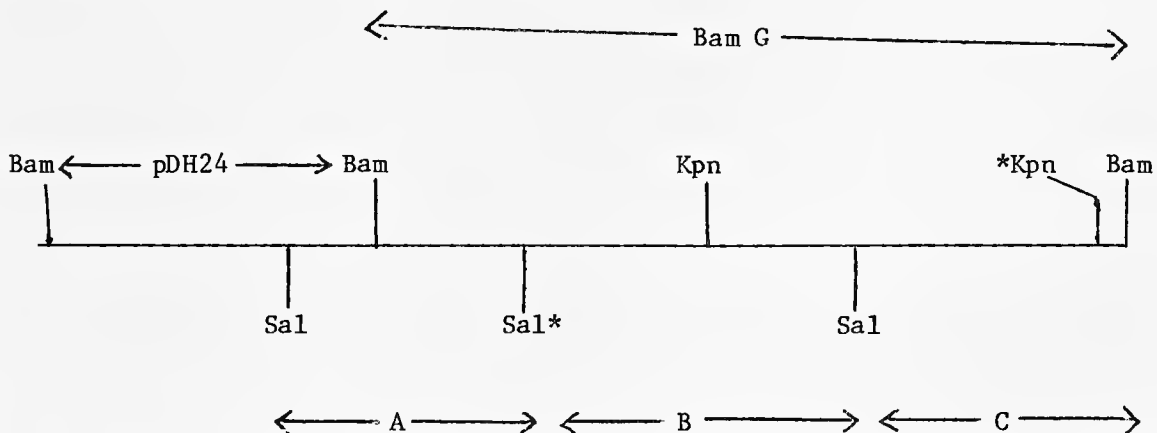
The Bgl II-I fragment (16.4 kb) which is contained within the Xba I-F fragment (22 kb) has also been shown to contain the B2 gene. The lambda (λ) vector Ch 28 was therefore used to clone the Bgl II-I fragment in the Bam HI cloning site by exploiting the fact that Bam HI cohesive ends are complementary to Bgl II cohesive ends. Recombinant DNA molecules produced from ligating Bam HI Ch 28 "arms" to the Bgl II-I fragment were packaged in vitro to give infectious lambda-phage which were subsequently plated on E. coli K12; strain LE 392. The efficiency of cloning was 9.5×10^3 pfu/ μ g HSV1 Xba I-F fragment, and a total of 3.3×10^3 pfu were obtained from 300 ng of Bgl II digested Xba I-F. The recombinant phage were screened for the presence of the Bgl II-I fragment by in situ hybridization using 32 P-labeled HSV DNA as a probe. Plaques hybridizing to the HSV probe were picked and amplified in 5 ml lysates, from which the phage DNA was subsequently purified and then digested with Bam HI and Bgl II/EcoRI. The DNA fragments were resolved by agarose gel electrophoresis and then blotted onto nitrocellulose and hybridized with 32 P-HSV DNA. The results from analyzing some 250 clones showed that none of the clones contained the authentic Bgl II-I fragment as judged by comparison to HSV1 virion DNA digested with Bam HI and Bgl II/EcoRI. The clones did, however, contain inserts to which the 32 P-HSV1 DNA probe hybridized. Since the purified Xba I-F fragment was at least 90% pure, it seemed unlikely that these clones represented other DNA fragments contaminating the Xba I-F fragment preparation. A more plausible explanation seemed to be that extensive rearrangement of the Bgl II-I fragment was occurring in the lambda-clones.

The HSV1 EcoRI-F fragment overlaps about 80% of the Bgl II-I fragment and could thus be used as a specific probe to isolate lambda-Ch 28 clones containing sequences homologous to Bgl II-I. The EcoRI-F fragment cloned in lambda-Ch 4A was obtained from Dr. George Vande Woude (NIH) and the EcoRI-F insert purified by agarose gel electrophoresis. The EcoRI-F fragment was labeled to high specific activity by "nick translation" with 32 P-dCTP and dGTP and hybridized to HSV1 DNA digested with EcoRI, Bam HI, Bgl II and XbaI. The results of this confirmed the specificity of the probe which was then used to screen the lambda-Ch 28 clones.

Eventually, 40 strongly hybridizing clones were purified by repeated cycles of replating and plaque picking and small scale lysates of these were prepared. The Ch 28 DNA was purified, digested with either Bam HI or Bgl II/EcoRI, resolved by agarose gel electrophoresis and finally blotted onto nitrocellulose paper. Hybridization of these blots with ^{32}P -EcoRI-F showed that most of the clones contained the authentic Bgl II-I fragment, which when digested with Bam HI gave the correct fragment pattern as determined by comparison to HSV1 DNA digested with Bam HI. Some of the clones, however, contained the Bgl II-I fragment in a rearranged form, confirming earlier results. From two of the clones, Ch 28-1 and 28-14, large scale lambda DNA preparations were made and the DNAs were labeled with ^{32}P by nick translation. Hybridization of these Ch 28 DNAs back to Bam HI, Xba I, and Bgl II digests of HSV1 DNA confirmed that they contained the authentic Bgl II-I fragment.

In order to facilitate identification of the B2 gene within the Bgl II-I fragment, Bam HI fragments derived from Ch 28-14 were sub-cloned into plasmid pDH 24. The plasmid vector and Ch 28-14 DNAs were digested to completion with Bam HI, and the vector DNA was further treated with bacterial alkaline phosphatase (BAP) to remove 5'-phosphate groups. The digested Ch 28 DNA was ligated to the BAP'd vector DNA, and the recombinant molecules used to transform *E. coli* HB 101. Since BAP'd vector molecules cannot recircularize alone, >90% of the ampicillin-resistant (Amp^{r}) transformants contained recombinant molecules. All five Bam HI fragments derived from Bgl II-I have been sub-cloned in pDH 24 and these migrate during electrophoresis as authentic HSV1 Bam HI fragments.

Recently, there has appeared in the literature data indicating strongly that the B2 gene lies in the largest Bam HI fragment derived from Bgl II-I; the Bam G fragment (8.1 kb) and thus this fragment has been characterized in some detail by restriction enzyme mapping and further sub-cloning. A schematic restriction enzyme cleavage map is shown below for the sake of clarity.



*New restriction enzyme sites, not present in the published restriction enzyme map.

The Bam-Sal fragments labeled (A) and (C) have now also been sub-cloned separately in pDH 24. The recombinant plasmid containing Bam G-(pDH BG-3) was digested to completion with Bam HI and Sal I and then religated and transfected into E. coli HB 101. Under these conditions, the internal Sal fragment C is not clonable since the vector DNA has one Bam HI end and one Sal I end.

Two different approaches are being used to identify the B2 gene fragment; the first, using an oligonucleotide probe generated from data obtained by sequencing the B2 glycoprotein, was described in last year's annual report. Results from work done by our collaborators, Drs. Richard Courtney and Jack Shively, however, indicate that the amino terminus of the B2 glycoprotein is blocked and, thus, cannot be sequenced from that terminus. Currently, they are attempting to digest the B2 glycoprotein with trypsin and obtain a purified tryptic fragment that can then be sequenced.

The second approach to obtaining the B2 gene involves hybridizing Poly A⁺ RNA from HSV-infected genes to cloned DNAs (Bam G, Sal A and C) immobilized on nitrocellulose filters and eluting the selected mRNAs that will then be translated in vitro. Identification of the B2 gene product will be done by immunoprecipitation using anti-B2 serum provided by Dr. Richard Courtney. These two approaches should allow us to isolate the B2 gene and to engineer its expression in a bacterial system.

In order to provide a source of defined HSV1 DNA fragments, a Bam HI "library" of the HSV1 genome has been constructed. HSV1 DNA was digested with Bam HI and the resulting fragments ligated to BAP-treated Bam HI digested plasmid pDH 24 DNA. The recombinant molecules were used to transform E. coli HB 101 to amp^r and those clones that were also tetracycline-sensitive (cloning in the Bam site of pDH 24 inactivates the tetracycline gene) were picked. Some 250 amp^r tet^s clones have been isolated and these are currently being screened to determine which of the HSV1 Bam fragments they contain.

Immunological Studies and Reactivation. Our work over the past year has mainly been concerned with development of a new animal model of latency utilizing passive immunization in mice. We have been able to look at important immunological factors in establishing and maintaining the latent state of the infection. We have recently found that the latent infection can be maintained in the absence of neutralizing antibody and that viral reactivation can be demonstrated by an increase in neutralizing antibody. Previously, reactivation was detected by recovery of virus from cell-free homogenates of epithelial or ganglion tissue. These reactivation studies were time consuming since treatment had to be delayed until the latent stage was established which usually meant one to two months.

To provide a rapid method of screening a variety of reactivation agents, passively immunized mice were utilized. In these studies, mice

were given high-titered rabbit anti-HSV serum at 3, 48, and 96 hours after inoculation with HSV. At the same time, experimental mice were treated with cyclophosphamide. The control group was inoculated and passively immunized, but given no treatment. Two and four days after inoculation, ganglia explants and homogenates were assayed in the experimental and control groups.

The effect of passive immunization was to bypass the acute stage of the ganglionic infection without actually preventing the infection. The test--a negative homogenate and a positive explant culture--was met as in standard latently-infected ganglia after acute infection. The acute stage was bypassed in about 80% of the mice. With cyclophosphamide treatment, however, the acute phase was bypassed in only 21% of mice. This result indicates that cyclophosphamide increases the degree of virus replication in ganglia.

To study the effect of anti-HSV antibody on latency, serum neutralizing antibody was measured various times after corneal or lip inoculation. Two groups of mice were used: passively immunized mice given rabbit anti-HSV serum i.p. 3, 48, 96 and 144 hours after inoculation, and control mice given non-immune serum on the same schedule. In control mice, the serum antibody titers were between 8 and 16 NU 7 days after inoculation, and 32-128 NU at 2, 3, and 4 months after inoculation. In contrast, antibody titers in the passively immunized mice were 128-256 NU 7 days after inoculation, 8-16 NU one month after inoculation, and less than 8 NU at 2, 3, and 4 months after inoculation. Despite the serum antibody titer of less than 8 NU, the infection was still in the latent stage in the passively immunized mice four months after inoculation (i.e., negative homogenate, positive ganglion explant cultures). This result indicates that serum neutralizing antibody does not play a critical role in maintaining the infection in the latent stage. To check the status of the infection, neutralizing antibody-negative mice were sacrificed four months after virus inoculation, and trigeminal ganglia were assayed by homogenization and explantation. These experiments showed that the latent infection was maintained (positive ganglionic explants and negative ganglionic homogenates).

The demonstration that antibody-negative, latently-infected (ANLI) mice could respond immunologically to HSV was exploited as a method for detecting viral reactivation. The lips of ANLI mice were traumatized by application of dry ice for 10 seconds, twice daily, for three 10-day courses. Antibody titer increased to greater than or equal to 16 in 90% of the traumatized mice. In contrast, an increase in antibody titer was detected in only 4 of 29 control mice, suggesting that spontaneous reactivation had occurred in these mice. No neutralizing antibody was detected in uninfected control mice subjected to dry ice trauma.

Reactivation by epithelial irritants proved to be effective also in corneally inoculated mice. Corneal scarification induced reactivation in

50% of mice that had been inoculated by the corneal route. We have shown convincingly that reactivation occurs only when the irritant is applied to the site of inoculation (lip in lip-inoculated mice and cornea in eye-inoculated mice). A formal possibility that latent virus persisting in the skin was being reactivated was ruled out by molecular hybridization experiments that failed to detect viral DNA in the lips of lip-inoculated latently-infected mice. Consequently, it had to be concluded that the latently infected cells in the ganglia of ANLI mice are confined to the area that corresponds to the inoculation site. This conclusion was proven correct by two sets of experiments. In the first experiment, the number of viral DNA copies in latently infected ANLI mice were determined and compared to the number of copies in mice that were similarly infected but given non-immune rabbit serum. ANLI mice had 0.08 ± 0.01 copies/cell; mice given non-immune serum had 0.17 ± 0.02 copies per cell. However, at five days post-inoculation, the animals given non-immune serum were at the acute phase of the infection, with 2-5 copies/cell, whereas ANLI mice had only 0.14 copies/cell. These results indicated that replication of the virus during the acute phase, which is precluded in passively immunized animals, produces a 10-20 fold excess of viral DNA over the amount found in ANLI mice. This excess is not reflected in the amounts of viral DNA observed when the mice given non-immune serum enter the latent phase, since the difference at this stage between these animals and ANLI mice is only two-fold. These results, indicating that replication of the virus during the acute phase has little effect on the number of viral DNA molecules found in the latent phase, support the view that latently-infected cells are confined to the area that corresponds to the inoculation site.

A more direct confirmation of this conclusion comes from dissection and explantation of selected portions of ganglia. Using a dissecting microscope, we were able to separate the section of the trigeminal ganglion with nerve cell bodies from the eye (GV-1) from the portion with nerve cell bodies from the lip (GV-3). These portions were explanted and scored for the presence of HSV CPE. In conventional latently-infected mice, both portions yielded virus, regardless of the route of inoculation. However, 79% of the corneally inoculated ANLI mice yielded virus only on the GV-1 section as compared to 11% in the GV-3 section; conversely, in lip inoculated ANLI mice, GV-3 was HSV-positive in 83% of the cases, and only 9% of the GV-1 yielded virus.

These results confirmed our prediction that in ANLI mice, the latent infection is confined to the area of the ganglion that innervates the inoculation site, as a result of antibody preventing the extracellular spread of virus in the ganglia. The implication, then, is that epithelial irritants induce reactivation by affecting nerve terminals.

HSV Sequences in Normal and Diseased Tissues from Humans. Herpes simplex virus possesses an exquisite tropism for the nervous system. Since the majority of the adult population has been exposed to or infected by HSV, it is of paramount importance to determine whether HSV,

or a portion of its genome, plays a role in the etiology of neurological diseases of unknown origin. A finding of this nature will provide a better understanding of the disease potential of this virus as a means to combat those diseases.

In the last ten years, a number of reports in the literature have demonstrated the potential for HSV-1 and HSV-2 to induce morphological transformation in rodent tissue culture cells. At least in one report, the transformed cells induce tumors at a high rate when injected into syngeneic hosts. Portions of the HSV viral genome have been shown to be associated with the DNA of the tumors, although the physical state of the viral DNA sequences is not known and the copy number per cell of the HSV sequences is variable and changes with passage history.

Epidemiological surveys have demonstrated an association between herpes simplex type 2 and squamous cell carcinoma of the cervix. Recent observations by others indicate that HSV-2 RNA sequences can be detected in cervical biopsy tissue from patients with diagnosed cases of cervical carcinoma, while in non-diseased tissue there is no evidence for the presence of HSV-2 nucleic acid sequences.

Several experimental strategies have been considered in developing assays to detect the presence of HSV nucleic acid sequences in diseased neural tissue from humans. The first, using Southern blotting technique, can be expected to detect viral DNA at the level of 0.5 copies/cell of any specific viral DNA sequence, representing 1% of the HSV genome. In situ hybridization techniques could be expected to detect HSV specific sequences at the level of one copy of viral DNA in 50 to 100 cells.

DNA from tissue culture cells and human tissues will be prepared from material which has been flash frozen in liquid nitrogen to minimize degradation. The DNA will be digested with restriction endonucleases and size fractionated on agarose gels. It will then be transferred to nitrocellulose paper and hybridized to high specific activity ^{32}P -HSV DNA or restriction endonuclease fragments prepared from bacterial plasmids into which have been ligated fragments of HSV DNA representing about 1 to 5% of the HSV genome. Detection of the hybrids will be by autoradiography. Positive control cell DNA will include HSV-infected rabbit, murine or monkey cells. Negative control cells will include uninfected monkey or rabbit DNA. Experimental tissue DNA will include human placental DNA and DNAs from normal or diseased neural tissue of human origin, such as neural tumors or tissue from patients with multiple sclerosis. In addition, tumors of the oral cavity will be examined. A positive control DNA probe will be the highly repetitive sequences of human DNA (termed the Alu family of DNA sequences) which are found in excess of 200,000 copies per cell. Negative DNA probes will include lambda DNA, bacterial plasmid DNA and bacterial DNA. These experiments, particularly those with normal cellular DNAs, will provide a background basis for determining whether there is any homology of the HSV genome with normal human DNA sequences.

In addition to the diseased neural tissue, we will examine a large number of human tumor cell lines of neural and oral origin for the presence of HSV-specific sequences using these same techniques.

In situ hybridization techniques to detect HSV-specific sequences are outlined below. Tissues or cells would be flash frozen in liquid nitrogen, thin sectioned with a cryotome, and fixed to slides. The tissue sections would then be hybridized (in situ hybridization) to ^3H -HSV DNA probes as listed previously and subjected to autoradiography. Positive quantitation would be based on a specific increase in the number of silver grains over cell nuclei. If HSV-DNA were associated with any of a number of possible neural and oral disease states (e.g., various types of primary tumors), one might expect a significant increase in the silver grain counts in positive tissue while negative or normal tissue would show no increase in silver grains. Human tissues to be examined include those from the brain stem and cerebral hemispheres (obtained at autopsy), normal and diseased tissue from the human brain (biopsy or autopsy tissue), tumors of the oral cavity, and mouse trigeminal ganglia from chronically and latently infected mice.

Summary and Future Studies

We have made considerable progress in several of the major areas of research in which we are involved. In the past, we detected reactivation by the recovery of infectious virus from ganglia at the latent stage of the infection. A major disadvantage of this method was that the mice must be sacrificed and only one point in time could be evaluated. In contrast, by monitoring serum neutralizing antibody in antibody-negative, latently-infected mice, we can carry out long-term experiments. Since antibody titers remain elevated for long periods of time, reactivation can be detected weeks or months after the actual reactivation event occurs. Thus, this new sensitive technique should facilitate our attempts to study biological mechanisms of reactivation.

Our efforts to identify the gene coding for the major antigenic determinant of the virus have narrowed it down to a fragment of the viral DNA with a coding capacity of not more than three genes. In the future, it can be expected that the individual gene will be identified and we will be able to start the second phase of this project, viz., insertion into an expression plasmid capable of producing large amounts of the viral protein in bacteria. Later, protection trials in mice will be initiated.

The integration of the viral DNA in the DNA of latently-infected mice has been confirmed using a second technical approach. During the next year, it may be expected that the joint viral-cell DNA sequences will be cloned by recombinant DNA techniques and the presence of co-valently joined molecules will be unambiguously proven.

Two areas of investigation proposed last year had to be postponed for lack of manpower. We propose to initiate them this year. They are: first, the examination of latently infected mouse ganglia by recombinant DNA techniques for expression of viral genes at the level of transcription and second, the extension of our studies in the animal model to the investigation of the naturally occurring herpetic infections in humans and to neurological diseases of unknown origin.

Publications

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRANURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00219-05 LOM																								
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SUMMARY OF WORK (200 words or less - underline keywords) <p> The possible role of <u>viruses</u> and <u>interferon</u> (IFN) in human immunopathologic process has been studied. We have extended our studies on the <u>immunoregulatory</u> actions of IFN by studying patients with <u>lymphoproliferative disorders</u>. We have observed a patient with a lymphoproliferative disease whose lymphocytes spontaneously produce IFN-γ in vitro, a phenomenon which has not previously been recognized. The patient has a proliferation of a mature <u>T cell</u> identified as a <u>Tg cell</u> with cytotoxic activity. The precise role of IFN in the pathogenesis and/or expression of this hemtologic disorder is uncertain at present. </p>																										

HERPES SIMPLEX VIRUS: Cell-mediated immune mechanisms, autoimmunity and interferon

Background and Objectives

During the past three years our knowledge of the human interferon (IFN) system has grown at an exponential rate. It is now clear that IFN is a cellular protein which can have a variety of biological actions. In addition to its antiviral actions, IFN can induce alterations in the synthesis of cellular macromolecules, alter plasma membrane conformation, inhibit cell multiplication and inhibit tumor formation. Moreover, new evidence strongly indicates that IFN modulates immunity by enhancing or depressing a variety of immune functions. In fact, IFN is now considered an immunoregulatory protein.

In man, there are at least three general types of IFN produced. These are now referred to as alpha, beta and gamma IFN. When viruses and a variety of other substances interact with leukocytes, alpha IFN is produced. When these same inducers interact with fibroblasts or epithelial cells, beta IFN is produced. As an integral part of their immune response, lymphocytes also produce an IFN that is called immune or gamma IFN. In this instance, the interaction of sensitized lymphocytes with antigens or antigen-antibody complexes results in IFN production. Among the types of IFN, the gamma IFN is the most active as an immunoregulatory protein and can even potentiate the biological actions of other IFNs.

The immune system consists of a series of complex responses by cells of the lymphoid system. These immune responses are regulated by both lymphoid cells and by soluble factors from lymphoid and other cells. Alterations in the regulation of immune responses could result in immunologically-mediated diseases such as immunodeficiency states, autoimmunity diseases and lymphoproliferative disorders. Viruses and/or IFN acting independently or in conjunction may induce aberrations in immunoregulation and thereby may play a role in the pathogenesis of immunologically-mediated diseases.

The objective of this research project is to study the possible role of viruses and IFN in immunopathologic processes.

IFN, an immunoregulatory protein, has multiple regulatory actions on lymphoid cells and immune responses. The excessive production or lack of production of immunoregulatory proteins can afford an opportunity to study normal lymphoid cell functions and normal regulatory mechanisms. During the past three years, we have described the presence of IFN in certain autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjogren's syndrome, scleroderma, and vasculitis. The highest levels of IFN were detected in SLE patients and serial serum samples showed a good correlation between the presence of IFN and disease activity. Serological studies demonstrated that the IFN is a leukocyte product and may be a mixture of alpha and gamma (immune) IFN.

Major Findings

IFN and immunologic disorders: During the past year we have extended our studies on the immunoregulatory actions of IFN by studying patients with lymphoproliferative disorders. We have observed a patient with a lymphoproliferative disease whose lymphocytes spontaneously produce IFN-gamma in vitro, a phenomenon which has not previously been recognized.

The patient is a 48-year old male who presented in August 1979 with fatigue and malaise and lymphocytosis. Liver biopsy and bone marrow biopsy demonstrated infiltration of lymphocytes and a diagnosis of chronic lymphocytic leukemia was made.

The patient's serum at the time of study showed a positive serum rheumatoid factor and a weakly positive anti-nuclear antibody. Serum protein electrophoresis revealed a normal profile. Serum Ig levels were 304 mg IgM/dl (Nl: 37-204), 1164 mg IgG/dl (Nl: 710-1540), and 382 mg IgA/dl (Nl: 60-490). High levels of serum immune complexes (56% Clq binding) were observed.

The hematologic profile at the time of the study showed a lymphocytosis associated with neutropenia. The patient's WBC count was 14,000 cells per mm³ with 92% lymphocytes and 6% neutrophils. Only 2% of the PB lymphocytes were B cells, whereas 95% were T cells. These were considered "low affinity" T cells because they would rosette sheep RBC only after overnight incubation at 4°C. 93% of the T cells expressed Fc receptors of IgG, and therefore, were designated T_G cells.

T cells were separated from non-T cells on the basis of low affinity E-rosette formation and density gradient centrifugation. Using this population of T cells, a histochemical and cell surface marker analysis was performed. These cells stained with beta-glucuronidase and acid phosphatase but not with terminal deoxynucleotidyl transferase, indicating that it is probably a mature T cell. By chromosomal analysis all of the cells were diploid.

We next examined the cell surface antigen phenotype of the patient's cells with monoclonal antibodies. Monoclonal antibody analysis as well as the lack of surface Ig indicated that the cells were negative for markers of monocytes and B cells. Analysis of the T cell surface antigen phenotype showed that the majority of the T_G cells were OKT3⁺, OKT8⁺. Again, these data add additional evidence that these are, indeed, mature T cells and taken together, the marker analysis and monoclonal antibody analysis clearly show that the patient had a proliferation of T_G cells.

The surprising and unique feature of this study is that the patient's cells spontaneously produced 80 to 320 units of IFN in vitro. This was observed in leukocytes collected and tested on 10 separate occasions during a 12-month period. In contrast, IFN was not detected in supernatant fluids tested from similarly treated cells obtained from 21 normal individuals, 8 other leukemia patients, 6 lymphoma patients, and 4 patients with SLE.

The antiviral activity in the supernatant fluids was characteristic of IFN. The fluids inhibited replication of virus on human, but not on mouse, cells. Moreover, the samples were not toxic for cells, and the antiviral activity was not lost after dialysis at pH 7.2, but was destroyed by trypsin. The IFN was further characterized by antibody and pH studies. Gamma IFN prepared by collecting supernatant fluids from concanavalin A stimulated PB leukocytes is not neutralized by either anti-alpha or anti-beta antisera and is labile at pH 2.0. Since the patient's lymphocyte supernatants had similar properties, we concluded that the leukocytes produced a gamma IFN.

We next attempted to precisely identify the cell producing gamma IFN. PB cells from the patient consisting of over 90% T_G cells produce IFN. When these cells are separated into glass adherent and glass non-adherent populations, only the non-adherent cells produced IFN. Moreover, incubation of these cells with the cytotoxic monoclonal anti-T antibody (D66) and complement resulted in the loss of IFN production. These studies suggested that cells bearing T-cell antigens either produced IFN themselves or were involved in the production of IFN.

Functional studies showed that the cells produced little or no Ig in vitro following PWM stimulation. This was not due to suppressor activity since the patient's cells did not inhibit normal cells from producing Ig in vitro. The cells had low levels of natural killer (NK) activity and normal or even elevated levels of antibody dependent cellular cytotoxicity (ADCC) activity. Thus, functionally, the patient's PB leukocytes did not display suppressor activity, had low NK activity and normal ADCC activity. Therefore, these cells are T_G cells with cytotoxic functions.

In summary, we report a patient whose cells spontaneously produce immune IFN in vitro. The patient had a proliferation of a lymphocyte which we identified as a T_G cell. This cell is a mature T cell which displays cytotoxic activity. The precise role of IFN in the pathogenesis and/or expression of this hematologic disorder is uncertain at present.

Interactions of IFN and other biological mediators (lymphokines):
The immune system consists of a complex regulatory process with interactions among T cells, B cells, macrophages and their soluble products. The soluble products derived from lymphocytes (lymphokines) can have a profound effect on the immune response. Therefore, we have studied the relationship between two of the major lymphokines, IL_2 or T cell growth factor and IFN-gamma.

Treatment of peripheral blood leukocytes with the T cell mitogen, concanavalin A, results in the production of IL_2 and IFN. Culture conditions that increase the production of IL_2 (PHA treatment), also increased the production of immune IFN. In contrast, the production of alpha IFN by leukocytes in response to virus was not associated with the generation of IL_2 . The close relationship in the production of IL_2 and IFN-gamma may mean that their production is linked in a sequential fashion.

Cytomegalovirus and immunologic disorders: Alterations of the host's immune response during viral infections have been observed with a variety of viruses. In fact, virus-induced immune dysfunction is especially common among viruses which persist in lymphoid cells. Cytomegalovirus (CMV), a member of the herpes virus group, is widespread in the human population. This virus can cause a mononucleosis syndrome in normal individuals and in patients who receive multiple blood transfusions. Several lines of evidence indicate that CMV interacts with lymphoid cells.

During the past few months we have initiated studies to investigate the relationship between CMV and immunologic disorders such as autoimmune diseases and lymphoproliferative disorders. Preliminary studies indicate that neutralizing antibodies are present in 40% of the normal individuals studied and in 50% of patients with Sjogren's syndrome and 65% of patients with SLE.

Viruses and IgE: We are also investigating the possible role of specific antiviral IgE antibodies in immediate hypersensitivity reactions. Mice have been immunized with herpes simplex virus and we have detected the presence of specific antiviral IgE antibodies by two assay methods: the antigen-induced response of histamine release from immunized mouse mast cells and the use of an indirect enzyme-linked immunosorbant (ELISA).

Significance

The implications of these findings to biomedical research can be divided into three categories: the nature of lymphoproliferative syndromes, methods to arrest or reverse leukemia processes and production of IFN-gamma for clinical trials.

The nature of this lymphoproliferative syndrome is uncertain at present. It is possible that this disease may not be a truly malignant proliferation of T cells but rather a disease caused by a disordered immunoregulatory mechanism. IFN is an immunoregulatory protein. In fact, it is known that IFN can trigger proliferation and differentiation of T cells. It is conceivable that IFN could be the underlying stimulus for the proliferation of T cells in our patient.

Studies on this patient may provide insight into methods to arrest or reverse the leukemic process. Neoplastic transformation can take place at any stage of lymphoid differentiation, from the stem cell to the mature T and B cell. It may be possible to make neoplastic lymphocytes respond to the normal regulatory influences of natural biologic modifiers resulting in a slower proliferative rate. Additional research along this line may reveal if IFN production is an appropriate biological signal which arrests the leukemic process in this patient.

Finally, IFN gamma is the most active of the IFNs as an immuno-regulatory protein and can even potentiate the biological actions of other IFNs. However, studies of gamma IFN have been hampered by the lack of sufficient quantities of this type of IFN. The finding of a cell programmed to produce IFN-gamma may enable us to use cell cloning and recombinant DNA techniques to obtain sufficient quantities of this IFN.

Future Plans

Our future plans for research on IFN are aimed at:

1. Identifying leukemic cells which produce IFN and determining if the production of this biologic modifier is related to an arrest of the leukemic process.
2. Propagating the IFN-gamma producing human T_G cell with IL₂ or hybridoma technology and using these cells to obtain large quantities of IFN-gamma.
3. Studying the immunoregulatory actions of human IFN by determining the effect of IFN on polyclonal B-cell activation and by determining the exact relationship between IFN-gamma and IL₂ production.

Our future plans for research on cytomegalovirus are aimed at:

1. Determining the anti-CMV antibody levels in patients with immunologic disorders.
2. Determining if CMV antigens are present in lymphoid cells from patients with immunologic disorders.
3. Identifying the lymphoid cells in which CMV replicates in the normal individual and in disease states.

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SUMMARY OF WORK (200 words or less - underline keywords) Induction and modulation of <u>virus and hormone receptors</u> are being studied in animal models to determine their roles in the pathogenesis of viral diseases as well as to characterize the influence of virus infections on pre-existing metabolic disease. In concert with these studies, clonal variants of pantropic virus are being studied in an attempt to relate specific diseases to differential expression of virus receptors in host tissues and specific antigenic determinants.																							

RECEPTORS, MEMBRANES AND DISEASE

Background

The surfaces of cells are known to possess receptors which determine if and how those cells will respond to viruses, hormones, and other cells. In recent years, the relationship between cellular receptors and disease has become increasingly evident. Most viruses must attach to a cellular receptor in order to infect a target cell, and the absence of an appropriate receptor can render a cell resistant to those viruses. Moreover, antibody to hormone and neurotransmitter receptors can produce serious disease as in extreme insulin resistance, Graves disease and myasthenia gravis.

In recent years, it has become evident that many diseases are associated with specific histocompatibility antigens. The HLA (human) and H-2 (mouse) major histocompatibility loci govern the expression of the strongest and perhaps the most important of the cell surface antigens. Insulin deficiency, diabetes mellitus, multiple sclerosis, and a host of rheumatological disorders have been found associated with increased representation of certain HLA haplotypes. It is not unreasonable to consider that an apparently minor change in one or more cell surface components could lead to altered cellular function and eventually to multi-systemic disease.

Our studies of the relationship between cellular receptors and diseases have concentrated on changes in hormone and virus receptors on normal and cultured cells in response to a variety of stimuli. Such stimuli include stimulation of cells in vivo and in vitro by mitogens (lymphocytes), irritants (macrophages), interferon (cultured human and murine cells), and virus infection (intact animals and cultured cells). We are also attempting to study the quantitative and qualitative expression of receptors for encephalomyocarditis virus on murine cells by using antireceptor antibodies, and by analysis of clonal variants of EMC virus that preferentially infect specific tissues.

Major Findings

Induction and Modulation of EMC Virus Receptors. Using a sensitive radioreceptor assay, we have examined the expression of EMC virus receptors on murine myeloid and lymphoid cells. Receptors for EMC virus were found to be present on the surface of resident peritoneal macrophages obtained from SJL/J mice. Thioglycolate broth-elicited peritoneal macrophages bound radiolabeled EMC virus at a rate two-fold greater than resident macrophages. This increase in binding of virus after activation was approximately of the same magnitude as the increase in cell volume. This suggested that the enhancement of EMC virus binding to macrophages might have been due to an increase in cell membrane surface area.

Unlike macrophages, resident splenic and thymic lymphocytes do not possess detectable EMC virus receptors, but they can be induced during blastogenesis following PHA, ConA and LPS stimulation. Both T and B cells are inducible at approximately the same rate. The induction requires DNA synthesis, and maximum levels of receptor induction are observed at 48 hours post-stimulation. In the case of lymphocytes, the appearance of receptors on the cell surface after exposure to mitogens is not due to the increase in cell surface, but due either to new synthesis of receptors or to a redistribution of cell components that previously covered receptors.

Although virus receptors increased after mitogenic stimulation, immunofluorescence revealed that only a small fraction (less than 2%) of the cells actually contained viral antigens, suggesting that virus receptors either were induced in only a small sub-population of lymphocytes or that post-attachment restriction prevented viral replication in a larger fraction of the cells. A survey of six cloned BALB/c T and B cell lymphomas frozen at different stages of differentiation showed that two of these lymphomas possessed EMC virus receptors, and only these two were susceptible to EMC virus infection, arguing that receptors are present at certain stages of cell differentiation.

In our experiments with continuous cell lines (Friend leukemia cells, FLC and BALENTL 13, a BALB/c T cell lymphoma), we found that rapidly proliferating cells also showed an increase in EMC virus binding, and that upon reaching a stationary density, the binding of viruses declined. Moreover, the increased EMC virus binding to FLC seen during logarithmic growth was completely blocked if the cells were grown in 2% dimethylsulfoxide (DMSO). At this concentration, DMSO induces erythroid differentiation in FLC, and as previously shown, murine erythrocytes, the endpoint cells of erythroid differentiation, lack EMC virus receptors completely. Thus, virus receptors can be increased or induced by various stimuli and the expression of EMC virus receptors may be related to the stage of differentiation or the phase of the cell growth cycle.

Interferon is a potent humoral factor with antiviral activity. Other laboratories have shown that interferon can induce an alteration in the expression of cell surface components on the membranes of treated cells (e.g., H-2 histocompatibility antigens on murine cells). We have tested murine (FLC and secondary mouse embryo fibroblasts) cells and human (HeLa and IM-9) cells after treatment with murine and human type 1 interferons in an attempt to determine if interferon treatment could alter the expression of EMC virus receptors as part of its anti-viral activity. The results of these experiments showed that in some cases at high doses of interferon, a reduction in EMC virus receptors was observed; however, the reduction appeared to be secondary to a suppressive effect on cell replication. Short of this, no direct effect of interferon on EMC virus receptors could be demonstrated.

Alterations in Insulin Receptor Activity Following Virus Infection.

For a hormone to exert its biologic effect, it must be synthesized, secreted, and transported to target tissues where it must then interact with specific receptors initiating a series of post-receptor events. Depending on the site of the underlying defect, abnormalities in hormonal action can be classified as occurring at the pre-receptor, receptor, or post-receptor levels.

Our studies on the relationship between cellular receptors and disease were focused on diabetes and viral infections. Alterations in insulin binding to receptors have been observed in a variety of states in which there is an alteration in glucose homeostasis. In these alterations, there are a number of physiological and pathological factors which regulate receptor concentration or affinity as well as affecting various post-receptor steps involved in insulin action. It is well established that viral infection may result in abnormalities of carbohydrate homeostasis. Recently, we showed that viral infections produced a decrease in the number of insulin receptors on cultured human cells in vitro, and suggested that a change in insulin receptor concentration may be one of the factors leading to abnormalities in glucose metabolism in individuals with viral infections. However, the in vivo effects of such agents have not been characterized. Further studies were carried out to define the effects of various virus infections and LPS on the insulin receptors in a mouse model system, as a probe of possible cell surface changes in viral infections.

Recent work in the LOM showed that using an in vitro radioreceptor assay with ^{125}I -insulin and human amnion (WISH) cells, both herpes simplex virus (HSV) and vesicular stomatitis virus produced a 50% decrease in insulin binding. On quantitative analysis, this decrease in binding was found to be due to a decrease in receptor concentration with little or no change in receptor affinity. The most likely explanation is that virus-induced changes in the plasma membrane alter or displace insulin receptors. These data suggest that in diabetic patients, abnormalities in glucose metabolism associated with some viral infections may be due, in part, to changes in the concentration of insulin receptors.

To evaluate more fully the effects of virus infections in vivo on insulin receptors, we have developed an assay system for ^{125}I -insulin binding to leukocytes and erythrocytes of mice which allows direct comparison of these tissues in studies on single mice. We found that mice infected with both highly diabetogenic (D) and non-diabetogenic (B) variants of EMC virus, HSV and lactic dehydrogenase virus (LDV), showed a transient increase in ^{125}I -insulin binding to receptors on splenic leukocytes, but little or no change on thymocytes, liver membrane preparations and peripheral blood erythrocytes. Administration of LPS also enhanced ^{125}I -insulin binding to splenic leukocytes.

The mechanism(s) for the increase in insulin binding is not known, however, since the increase in insulin binding following infection appears

to be limited to the leukocyte population, and since insulin receptors are known to be induced on T and B lymphocytes after their activation with appropriate mitogens or antigens, mitogenic stimulation of quiescent immune cells may be one of the explanations for the increase in insulin binding.

Our studies suggest (1) that viral infections and bacterial toxins can activate leukocytes to express increased numbers of insulin receptors which might alter the distribution of insulin and indirectly cause abnormalities in carbohydrate metabolism, and (2) that if patients have been infected with viruses or exposed to other mitogenic stimuli, such as might occur in patients with immune disease, insulin binding to leukocytes may not accurately reflect the insulin receptor status on other target organs (e.g., liver, erythrocytes).

Anti-receptor Antibodies. We have previously described the kinetics of binding of EMC virus to receptors on murine and human cells and have shown that the binding to murine receptors is characterized by a high rate of dissociation of the virus from the virus-receptor complex. The receptor assay uses radiolabeled EMC virus and is sensitive and specific; however, in some applications the rapid dissociation limits its usefulness. In an attempt to circumvent this problem, we are making use of the BALENTL 13 cells. As we have shown, this T cell lymphoma is rich in EMC virus receptors while normal murine T and B cells lack receptors. Thus, we have used BALENTL 13 cells as an immunogen to prepare a rabbit antiserum against the receptor. After extensive absorptions using BALB/c splenic and thymic lymphocytes and BALB/c erythrocytes (also receptor negative), this serum is able to block EMC virus binding to receptors on murine and human cell lines to the extent of 4 to 10-fold at a dilution of 1/10.

Although the results to date are encouraging, the titer of the serum is low (in part, due to the vast number of receptors per cell, greater than 10^5 , which must be blocked), and much work remains to show the true specificity of this serum. At the same time, we are attempting to raise anti-idiotypic sera against monoclonal anti-EMC virus immunoglobulins in order to obtain immunoglobulins whose Fab fragments will react with EMC virus receptors. As reported by others, this approach has been successful with several antigens including insulin and retinol binding protein.

Variants of EMC Virus. We have previously described the isolation of diabetogenic (D) and nondiabetogenic (B) variants of EMC virus. We have attempted to obtain and characterize additional variants with tropisms for specific tissues. These variants have been cloned from a heart-passaged EMC virus stock, and five additional variants have been partially characterized. All grow to high titers (10^8 to 10^9 plaque-forming units/ml) in vitro.

One of the five, clone 82A, is comparable to the D variant and induces diabetes in 100% of infected SJL/J mice. Clone 5A, like the B variant is nondiabetogenic, however, it replicates to 10- to 50-fold

higher titers than the B variant, and may lack the potent interferon-inducing activity of the B variant. Clones 125A and 162A induce moderate diabetes in SJL/J mice but also appear to cause a fatal myocarditis in about half of the animals. Clone 221A causes a fatal myocarditis in virtually all infected animals and may also have a mild diabetogenic effect.

By neutralization with a polyclonal rabbit antiserum and one monoclonal antibody against the D variant, all of these variants share a single serotype. This is a known characteristic of viruses related to EMC (i.e., Mengo virus, ME virus), however, as more monoclonal antibodies become available, it may be possible to relate the tissue tropisms of these variants to specific antigenic determinants.

Significance to Biomedical Research

To a great extent, receptors are key intermediates in the response of cells to hormones, the infection of host cells by viruses, and the immune response. In man as well as in animal models, many debilitating diseases have been shown to be related to decreased number or function of receptors. Other diseases are associated with known cell surface antigens, and still other diseases are caused by agents that require an appropriate surface receptor. In some cases, the relationship between the receptor and the disease has been characterized (e.g., adult obesity and insulin resistance). However, we are still left with a large degree of ignorance concerning the role of the cell surface in determining susceptibility to disease. By the appropriate study of selected membrane receptors, the relationship of receptor function and/or dysfunction to disease may be illuminated.

Course of Future Studies

In the upcoming year, major effort will be made to characterize EMC virus variants and the receptors for them. The existence of these variants provides an animal model of a poorly understood characteristic of human Coxsackievirus infections--that a single serotype of virus can induce different diseases in different individuals. It would be useful to know whether this is due solely to virus-specific factors or host factors including, but not limited to, receptors.

We will continue our studies of the effect of virus infections on receptors for polypeptide hormones in order to define the hormonal dysfunction. In addition, the possible diagnostic significance of changes in insulin binding to peripheral leukocytes of patients with viral infections will be investigated.

Publications

1. McClintock, P. R., Billups, L., and Notkins, A. L.: Receptors for encephalomyocarditis virus on murine and human cells. Virology 106:261-272 (1980).

2. Shimizu, F., Hooks, J.J., Kahn, C.R., and Notkins, A.L.: Virus-induced decrease of insulin receptors in cultured human cells. J. Clin. Invest. 66:1144-1151, 1980.
3. Shimizu, F. and Kahn, C.R.: Insulin radioreceptor assay on murine splenic leukocytes and peripheral blood erythrocytes. Endocrinology (in press) 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 DE 00309-01 LOM
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Hybridomas: A probe to study viral and other diseases		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Haspel, M.V. Prabhakar, B. Oh, C.S. Yoon, J.W. Onodera, T. Kende, M. Notkins, A.L.	Sr. Staff Fellow Staff Fellow Visiting Fellow Research Microbiologist Visiting Associate Expert Medical Director	LOM NIDR LOM NIDR LOM NIDR LOM NIDR LOM NIDR LOM NIDR LOM NIDR
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Oral Medicine		
SECTION		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland		
TOTAL MANYEARS: 8.00	PROFESSIONAL: 4.05	OTHER: 3.95
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<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <u>Monoclonal hybridomas</u> have been developed against a number of <u>viruses</u> including <u>Coxsackie B4</u> <u>Encephalomyocarditis(EMC)</u> and <u>Mengo</u> . These <u>monoclonal</u> <u>antibodies</u> will be used as probes of <u>antigenic variation</u> in laboratory strains of differing <u>tissue tropism</u> as well as of recent clinical isolates. Non- neutralized variants will also be isolated and characterized. <u>Autoimmune</u> <u>antibody</u> producing hybridomas have been developed from splenic leukocytes of <u>reovirus type 1</u> infected mice.		

HYBRIDOMAS: A PROBE TO STUDY VIRAL AND OTHER DISEASES

Introduction

Specialized cells that elaborate products such as specific antibodies or hormones replicate poorly, if at all, in culture. It is now technically possible to fuse a non-replicating antibody producing cell with an HGPRT⁽⁻⁾ mutant myeloma cell. Only the successful hybrids can replicate in medium containing aminopterin supplemented with hypoxanthine and thymidine. These "hybridomas" are then screened for synthesis of specific antibodies and subsequently are cloned. Each monoclonal hybridoma produces antibody directed against a single antigenic determinant. These monoclonal antibodies are unsurpassed as probes of minute antigenic changes in viral and other antigens which are not detectable by monospecific sera. The monoclonal antibodies can also be used to select for viral variants. Furthermore, hybridomas produce these monoclonal antibodies in large quantities. The conceptual and technical basis of antibody producing hybridomas should be directly applicable to other cell systems such as hormone producing endocrine cells, neurotransmitter and neurohormone producing cells.

Coxsackievirus

Objectives. To produce a panel of monoclonal antibodies against Coxsackie B4 virus and to use them to delineate the antigenic composition of these viruses. This information would be useful in establishing a correlation between antigen specificities of the viruses and their tissue tropism.

Major Findings and Future Plans. Since Coxsackie B4, as well as other related viruses, can cause different clinical syndromes, such as meningoencephalitis, hepatitis, diabetes, myocarditis, etc., it is, therefore, very essential to understand the antigenic nature of these viruses. However, it has not been possible to distinguish, antigenically, these variants by previously available methods. Therefore, delineation of antigenic moieties on each of the subtypes and especially on those that are isolated in association with different clinical syndromes would require more specific probes, such as, monoclonal antibodies which differentiate minor antigenic differences.

Different viruses have different abilities to induce an immune response; therefore, we have concentrated our efforts in making monoclonal antibodies against Coxsackie B4 virus. Though the techniques for producing larger numbers of hybridomas secreting specific antibodies have been well established, it was essential to optimize the procedure for this particular antigen. Some of the variables that we had to contend with are: dose of antigen, route of immunization, the protocol for fusion and culture conditions. So far, we have tested more than one thousand culture supernatants and have found approximately 60% of them to be positive in a microneutralization test. At the present time, we

have already cloned more than 200 hybridomas and we are in the process of testing the clones. Initial screening using either a radioimmunoassay or microneutralization test has identified at least 90 monoclonal antibodies arising from 21 different hybridomas. These will be recloned and further tested for their specific reactivity.

We are planning to make monoclonal antibodies against other members of the Coxsackie B group so that a panel of monoclonal antibodies with different specificities is established. Such a panel of antibodies would allow us to define the finer antigenic specificities of these viruses. Attempts will be made to correlate certain antigenic specificities with the ability of the virus to bind to and replicate in certain types of cells (using receptor binding assay developed in our laboratory). This information, we believe, will allow us to establish a relationship between the expression of certain antigens on the virus and their tissue tropism.

Monoclonal Antibodies to the Diabetogenic Encephalomyocarditis Virus (EMC-D) Virus)

Objective. To develop monoclonal antibodies directed against the diabetogenic clone of EMC virus. To utilize this antibody panel to probe for similarities and differences among related viruses (non-diabetogenic EMC-B and mengo viruses).

Major Findings and Future Plans. Hybridomas have been established that produce antibodies to EMC-D virus. One hybridoma clone produces IgA which neutralizes EMC-D virus, and the other clone produces IgG and IgM. Studies are in progress to determine if the latter clone is composed of two different kinds of clones or not. Also, dozens of other clones are now being studied to determine whether or not they secrete antibodies. These antibodies will enable us to identify antigenic variants and efforts will be made to relate antigenic differences to virulence.

Mengo Virus

Background and Objectives. Mengo virus is serologically indistinguishable from EMC virus, but yet they differ in tissue tropism. Monoclonal antibodies can delineate antigenic differences not apparent with monospecific polyclonal antibodies. These differences in antigenic determinants may then be correlated with the differences observed in vivo.

Major Findings and Future Studies. Of the 19 hybrids isolated from the first Mengo fusion, 2 strongly bound Mengo virus in a radioimmunoassay (3 additional hybrids are of low reactivity). The supernatants of the monoclonal hybrids have been tested against EMC virus, one reacts very strongly with EMC ($\frac{\% \text{ EMC bound}}{\% \text{ Mengo bound}} = 2.2$), while the other binds much less EMC than Mengo virus ($\frac{\% \text{ EMC bound}}{\% \text{ Mengo bound}} = 0.20$). Therefore, we have mono-

clonal antibodies that distinguish between Mengo and EMC viruses in an RIA. Thus, the value and importance of monoclonal antibodies in identifying viral variants is confirmed.

The specific antigens for each of the monoclonal antibodies need to be determined. The binding of these antibodies to variants of EMC and Mengo that differ in pathogenic potential will also be examined. Furthermore, additional fusions are being done and the hybridomas are being screened.

Autoantibodies

Objectives. Mice infected with reovirus type 1 develop autoantibodies that react with normal anterior pituitary and islets of Langerhans. Antibodies directed against growth hormone and insulin have been identified. Our objectives are to fuse spleen cells from autoimmune mice with mouse myeloma cells to produce autoantibody producing hybridomas. These monoclonal antibodies will be used to identify both common and unique auto-immunogens in different animals. Furthermore, hybridomas may identify autoantibodies not readily detected in whole sera. In addition, autoantibodies may serve as useful reagents in the detection and purification of hormones and other antigens.

Major Findings and Future Studies. Thus far, two strongly reacting autoantibody producing hybridomas have been isolated. One reacts with the pancreas while the other reacts with the anterior pituitary (four additional hybridomas exhibit low activity against the pancreas). The anti-pancreas hybridoma supernatants react with glucagon-containing α cells and its activity is significantly reduced by absorption with glucagon. Furthermore, staining of α cells by sera from mice with autoimmune disease is relatively weak if detected at all. Antibody to glucagon has not readily been produced in rabbits. The availability of a strongly reactive glucagon-directed antibody is of great value for detection and immunoabsorption purification of this hormone.

The antibody directed against the anterior pituitary does not appear to react with growth hormone. Taken in toto, these findings indicate that hybridomas may demonstrate antibodies not readily detected in the animals. Accordingly, we have broadened our screening procedure to include other organs such as brain, gastric mucosa, skin, thyroid, salivary glands, lungs, and adrenal glands. In the future, we will continue to utilize hybridoma technology to: 1) detect autoantibodies to a variety of organs; 2) compare specificity of hybridomas from different animals, and 3) utilize, and make available to other researchers, these monoclonal antibodies as probes.

Fusion of Endocrine Cells

Objectives. The objective of this project is to apply the rationale behind monoclonal antibody hybridomas to hormone-producing cells; that is, to fuse a non-replicating or poorly replicating hormone-producing

cell with a non-producer tumor cell. In this manner, large quantities of hormone-producing cells can be obtained for studies of hormone synthesis and secretion, and these cells can serve as sources of hormone for purification. In addition, these hormone hybridomas will provide insight into the possible existence of monoclonal hormones.

Major Findings and Future Studies. Efforts are in progress to select mutants resistant to 6-thioguanine ($6-T_G$) (defective in the enzyme HGPRT) or BUdR (defective in the enzyme TdK). These cell lines will be fused and the hybrids will then be selected in HAT medium. To date, two cell lines, C15F (insulin-producing) and GH3 (growth hormone producer), have been developed that are resistant to $6-T_G$. Work is in progress to select $6-T_G$ resistant somatostatin, ACTH, steroid and non-producer (insulinoma) cell lines. Difficulty has been experienced in obtaining BUdR resistant cells, probably due to the relative infrequency of TdK mutants. Cells will be mutagenized with methane-sulfonic acid prior to selection with BUdR.

GH3 cells ($6-T_G$ resistant, chloramphenicol sensitive) were fused with histamine secreting rat mastocytoma cells (chloramphenicol resistant, $6-T_G$ sensitive). While the mastocytoma cells were eliminated by the thioguanine in 1 to 2 weeks, the growth hormone-producing cells died out only after 3 to 4 weeks. After the death of both parents, colonies of presumptive hybrids grew in the hybridization wells. Colonies grow very slowly without attaining more than 30% to 40% confluency which varies from assay to assay. Full confluency was attained only when media without inhibitors were used. Four cell lines were established from the presumed hybrids, with histamine levels comparable to the parent mastocytoma line. The cells multiply fast and morphologically resemble the mastocytoma cells. In three of the cell lines, the growth hormone assay was positive. In a repeated assay, the presence of hormone was not confirmed. Confirmation of the presence of growth hormone, as well as cloning and chromosome counting, is in process. It may be possible that positive hybrids can produce growth hormone but are unable to secrete it into the media. Therefore, cell extracts will be assayed for unreleased growth hormone.

Efforts will continue to isolate a panel of $6-T_G$ and BUdR-resistant hormone-producing cells. Reciprocal fusions will then be attempted. If the resulting hybridomas between non-producer and producer parents continue to synthesize hormones, fusion of non-replicating cells obtained from endocrine organs and tumor cells will be the next step.

Summary and Future Studies

Over the past year, monoclonal antibodies have been developed against Coxsackie B4, EMC, and Mengo viruses. These monoclonal antibodies will be used to study viral variations. A monoclonal hybridoma has been isolated that reacts strongly with Mengo but weakly with EMC virus, thus distinguishing between two heretofore serologically identical viruses.

In addition, the monoclonal antibodies will be used to select for viral variants. Variations in viral antigenic determinants will be compared with the properties of tissue tropism and virulence.

Fusion of unmanipulated spleen cells from autoimmune mice with mouse myeloma cells has yielded hybridoma that synthesizes autoantibodies. The autoantibodies thus far isolated are directed against glucagon and the anterior pituitary. Hybridomas will be used to explore the spectrum of autoantibodies.

Efforts are underway to develop 6-TG and BUdR resistant hormone-producing cells so that selection for hybrids may be readily made in HAT medium. In this manner, we hope to apply hybridoma technology from antibody to hormone-producing cells.

ANNUAL REPORT OF THE
CLINICAL INVESTIGATIONS AND PATIENT CARE BRANCH
NATIONAL INSTITUTE OF DENTAL RESEARCH
SUMMARY STATEMENT 1980-1981

The Clinical Investigations and Patient Care Branch conducts research related to the diagnosis, prevention, and treatment of oral and dental diseases. It also provides support and facilities for clinical research programs of other Branches and Laboratories within the Institute. In addition, the Branch offers consultation on diagnosis and treatment to Clinical Center patients. Preventive dental care and restorative treatment are offered in the Dental Clinic, Clinical Center to selected medically compromised patients.

The Branch has as its major goal the development of programs in which the dental care for the unique patient population of the Clinical Center is integrated not only with the conduct of clinical research, but also with the training of clinicians and other dental staff in the delivery of care and in the methodology of clinical research.

Work started last year to define the roles and responsibilities of the Dental Clinic in patient care has been continued through new avenues of communication with the medical staff of the various Institutes and of the Clinical Center. Staff dentists now participate in rounds and patient discussions in two Institutes (NCI & NINCDS), and are consulted routinely on proposed commitments of dental care. In order to improve and standardize care a Clinical Manual is under preparation. The Manual will bring together all policies, forms and descriptions of standard operating procedures used in the Dental Clinic.

Recently, an in-depth analysis has been performed by outside consultants on the administrative management of the Dental Clinic and the systems for appointment scheduling, clinical records, recall and referral of patients. The analysis has resulted in two reports with proposals and plans for an improvement of existing systems. One major recommendation was that a Clinic Chief be appointed who would be located in the dental clinic. In response to that recommendation, the Institute has established two new sections within the Branch, the Patient Care and the Clinical Investigations Section. Further, Dr. Michael Roberts, formerly Chief, Dental Staff, Bureau of Medical Services, Washington, D.C., has been appointed Chief of the Patient Care Section with full responsibility for the efficient and effective operation of the dental clinic. Dr. Roberts assumed his new duties on August 3, 1981. Besides his day-to-day duties as clinic chief, Dr. Roberts will be deeply involved in the planned major renovation of the clinic itself.

The Clinical Director and Branch Chief, Dr. Karl-Åke Omnell, resigned June 30 to assume a position as Dean of the School of Dentistry, the University of Washington, Seattle. A new Clinical Director and Branch Chief, Dr. Bruce Baum, presently with the NIA, has been identified. He will assume his new duties on January 1, 1982. In the interim, the Director of Intramural Research has been serving as Acting Clinical Director.

An area of particular concern to the Branch has been the Clinical Dental Associate, now Dental Staff Fellow program. Under the present guidelines, the Associates divide their time (60/40) between research and patient care during the two years of their appointment. This approach has created uncertainty in both areas, and the consultants strongly recommended that the dental staff fellows spend their first year primarily in clinical work, while they are provided an opportunity to do virtually full-time research of their choice the next one or two years. Since this recommendation echoes the Institute's own ideas, efforts are already under way to restructure the program.

Two staff dentists have been involved in clinical research projects. Dr. Agnes Donahue, Staff Fellow, has conducted a retrospective study on the epidemiological and clinical parameters of jaw lesions in Burkitt's Lymphoma in the American population. The study is described in a separate report (Z01 DE 00320-01).

Dr. Thomas Rams, Staff Fellow, has been working with Dr. Paul Keyes, Laboratory of Microbiology and Immunology, NIDR, on analyzing the data from Dr. Keyes' long term study on the effect of modified treatment modality on periodontal disease (Z01 DE 00-9607).

Dr. Karl-Åke Omnell has conducted experimental salivary gland studies in collaboration with Dr. Eva Quarnstrom from the Laboratory of Biological Structure, NIDR. A technique has been developed making it possible to infuse contrast media and other liquid media into the natural orifice of the duct from the submandibular gland in rats. The technique offers previously non-existing possibilities to investigate the long term effect of different infused media upon the morphology of the gland as well as upon the composition of the saliva. Two other studies have dealt with the long term effect of infusion of water soluble contrast medium upon the ultrastructure of the rat submandibular gland and the composition of saliva, respectively. The three projects will be reported in detail from the Laboratory of Biological Structure (Z01 DE 00028-14).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER <div style="text-align: center; font-weight: bold;">Z01 DE 00320-01 CI</div>
PERIOD COVERED October 1, 1980 - September 30, 1981		
TITLE OF PROJECT (80 characters or less) Survey of Jaw Lesions in Burkitt's Lymphoma in the NIH Population		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between;"> Donahue, Agnes H. Staff Fellow IR NIDR </div>		
COOPERATING UNITS (if any) NCI/POB		
LAB/BRANCH Clinical Investigations & Patient Care Branch		
SECTION Patient Care Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: <div style="text-align: center;">1/15</div>	PROFESSIONAL: <div style="text-align: center;">1/15</div>	OTHER:
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS Chart review only </div>		
SUMMARY OF WORK (200 words or less - underline keywords) The <u>epidemiological</u> and <u>clinical parameters</u> of <u>jaw lesions</u> in <u>Burkitt's Lymphoma</u> in the <u>American population</u> are being studied retrospectively. Techniques include <u>chart review</u> of <u>demographic</u> and <u>clinical data</u> of all patients admitted to the NIH Clinical Center with a confirmed diagnosis of Burkitt's Lymphoma who have primary or metastatic jaw disease.		

Introduction:

Now that Burkitt's Lymphoma has been identified and studied in American populations, several striking differences from the African form of the disease have been described. One difference which is of particular interest to Dental Science is the incidence of jaw lesions. Jaw lesions occur in more than 50% of African Burkitt's cases while they represent only 5% of lesions in the American populations.

Approximately one fourth of all cases of Burkitt's Lymphoma confirmed in the United States, Canada, Mexico and South American countries have been treated or evaluated at the NIH Clinical Center. Such population concentration offers a unique opportunity to review and explore the epidemiological and clinical parameters of jaw lesions in American Burkitt's Lymphoma.

Project Description

I. Objectives:

Three primary objectives are identified as follows:

1. To study the epidemiological parameters of jaw lesions in American Burkitt's Lymphoma with respect to prevalence; incidence and age, sex, racial, economic and geographic distribution.
2. To describe the clinical history and clinical course of primary and metastatic jaw lesions with respect to initial clinical presentation, clinical and radiographic appearance, clinical course, prognosis with respect to therapy and prognosis with respect to survival.
3. To compare and correlate epidemiological and clinical data extracted from studies of jaw lesions in the American patients with known data from the African experience.

II. Methods Employed:

A selective review of all referring, admissions and clinical descriptive data for all patients with confirmed Burkitt's Lymphoma and known jaw involvement. A selective review of all available radiographic and other adjunctive diagnostic material (i.e. dental and other radiographic projections, CT and gallium scans, etc). A review is made of all related pathology and autopsy reports describing tumor status in the jaws and teeth.

III. Major Findings:

There is a 16% incidence of jaw lesions in the NIH Burkitts Lymphoma population over the past 13 year period. The incidence of jaw lesions during the same period in the general American Burkitts population is reportedly 5%. In both the general American and the NIH Burkitts populations there are two peak age ranges of high incidence (3-7 years and 19-24 years). This bimodal

trend is different from the African Burkitt's experience where jaw disease is seen most prevalently in children under 5 years with continuous decrease in incidence with increasing age of presentation.

Variations in clinical presentation and clinical appearance are noted between the two age groups. Children 3-7 years old present with a more classical appearing jaw lesion characterized by rapid expansion of the involved jaw, marked facial asymmetry and notable bony destruction on radiographic survey. Patients in the older age group (19-24 years of age) frequently present with facial pain usually described as a "toothache". Swelling is less pronounced and often confined to intra oral structures. The initial radiographic picture is less alarming, often appearing only as a thickening of the periodontal ligament space. Tooth removal does not relieve the pain. The lesion rapidly becomes exophytic and progresses to extensive bony destruction after the symptomatic tooth is extracted.

IV. Significance to Biomedical Research and the Program of the Institute:

Burkitt's patients over 12 years of age with primary jaw lesions usually present with odontalgia and clinical findings often reminiscent of routine dental disease. Ninety percent of older patients in the study first sought dental care for management of their symptoms. Since Burkitt's tumor is extremely rapid growing with only moderate prognosis when tumor therapy is expeditiously initiated, the time lapse from diagnosis to tumor management is critical to survival prognosis. A study of the clinical course and epidemiology of jaw lesions in American Burkitt's lymphoma is essential to describe and delineate the diagnostic criteria, natural history and clinical course of the disease. It will also provide a descriptive profile of the affected population. Such information is invaluable to rapid diagnosis and hence improved patient prognosis. Results of this exploratory research endeavor can benefit patients, as well as the science and clinical practice of dentistry.

V. Proposed Course:

The prospective phase will concentrate on defining the clinical parameters and describing the protracted clinical course of jaw lesions in Burkitt's patients admitted to the Pediatric Oncology Branch of the NCI. It is proposed to monitor bony changes of those Burkitt's patients with jaw involvement before, during and after chemotherapy using digital subtraction radiography.

Publications: None

Report of the Diagnostic Systems Branch
National Institute of Dental Research
Summary Statement FY 1981

The Diagnostic Systems Branch (DSB) was renamed from the Clinical Investigations Branch (CIB) to more specifically describe its research activities, and to avoid any possible confusion with the newly organized Clinical Investigations and Patient Care Branch.

The components and research thrust of DSB remain largely unaltered by this change in name, but increased emphasis has been placed this year on systematic analysis of factors influencing diagnosis of oral and related systemic disorders.

The Branch is comprised of two sections, the Oral and Pharyngeal Development Section (OPD) under Dr. James Bosma, and the Diagnostic Methodology Section (DMS) headed by Dr. Richard L. Webber. As in previous years, these sections work largely independently. OPD emphasizes the study of form, development, and function of oral and pharyngeal tissues through detailed anatomical measurements. DMS approaches the study of oral disorders with more of a systems orientation which is grounded in image processing and information theory. Together the sections compliment each other by providing a multidisciplinary approach to diagnostic problems of mutual interest.

Research priorities have required that OPD consolidate efforts to characterize the oropharyngeal complex in clinically meaningful ways. The first impact of this change in emphasis has been to initiate the phasing out the "taste" program including all related research pertaining to salivary biochemistry and threshold psychophysics.

Existing studies in these areas are being completed and efforts to relocate associated personnel into areas which compliment their research interests and aptitudes are under way.

In the meantime, new collaborative initiatives with Johns Hopkins Hospital and other prestigious clinical programs have been established in an effort to focus research on specific clinical needs of patients suffering from functional impairment of the oropharyngeal complex. To this end, Dr. Bosma has been active in establishing formal bases for interdisciplinary study in association with gastroenterologists, radiologists, E.N.T. specialists, and other clinicians with research interests in this area. In addition to these activities, OPD continues its commitment to making scholarly contributions to anatomic and developmental literature.

DMS is primarily concerned with the systematic study of diagnostic images. This involves analysis of spatial and temporal relationships of multidimensional sources of diagnostic information such as radiographs and CT scans. Activities are balanced between the investigation of new bases for quantitatively classifying information of diagnostic interest, and the study of alternative technology via computer simulation and development of prototype systems. Most emphasis has been placed on developmental studies of factors limiting diagnostic performance obtainable from sequentially obtained radiographs. This effort is in response to requests by many institutions and research groups concerned with dynamic changes in mineralization of teeth and supporting tissues.

Of particular interest is a digital-image, subtraction technique recently developed by DMS personnel for detecting radiologic changes which otherwise would be invisible. This work also compliments preliminary studies done in collaboration with the X-ray Physics Group at the National Bureau of Standards which

under a NIDR Interagency Agreement will be collaborating in the development of hardware designed to assure accurate reproduction of exposure geometry from one examination to the next in dental radiography. Both of these efforts anticipated the research recommendations of the consensus workshop on dental radiology sponsored by the National Center for Health Care Technology held in late June which explicitly acknowledged the need for, more research in the area of digital radiography, and for development of better methods for controlling exposure geometry.

Work also continues on the determination of theoretical limits underlying the transfer of diagnostic information in quantum-limited systems. The radiologic effect of prior probability of lesion occurrence, as well as the impact of the underlying distribution of lesion sizes, have been taken into account by an extension of Bayesian principles into information theoretic measures of diagnostic performance. As a result it is possible to extend principles underlying ROC analysis to multialternative, and even continuous sample spaces.

Work continues on the application of symmetric-axis geometry to the description of the mandible. Ambiguities in the abstraction of shape data from cephalograms prior to application of symmetric-axis analysis have complicated statistical interpretation but independent longitudinal studies appear to confirm previous findings based on the Broadbent-Bolton data base.

In keeping with the shift in priorities underlying the reorganization of OPD DMS, likewise, is planning to focus more heavily on applied research which facilitates understanding and performance of specific diagnostic tasks. To this end, future efforts will concentrate on task-specific, person-machine systems having performance limited by sampling strategy, information capacity, or the mode of information display.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00048-10 CI						
PERIOD COVERED October 1, 1980 - September 30, 1981								
TITLE OF PROJECT (80 characters or less) Anatomical Studies of the Head								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Bosma, J. F.</td> <td style="width: 33%;">Chief, Oral Pharyn Dev Sec</td> <td style="width: 33%;">NIDR DS</td> </tr> <tr> <td>Murayama, D.</td> <td>Illustrator</td> <td>NIDR DS</td> </tr> </table>			Bosma, J. F.	Chief, Oral Pharyn Dev Sec	NIDR DS	Murayama, D.	Illustrator	NIDR DS
Bosma, J. F.	Chief, Oral Pharyn Dev Sec	NIDR DS						
Murayama, D.	Illustrator	NIDR DS						
COOPERATING UNITS (if any) Division of Research Services, MAPB								
LAB/BRANCH Diagnostic Systems Branch, NIDR								
SECTION Oral and Pharyngeal Development								
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205								
TOTAL MANYEARS: .80	PROFESSIONAL: .40	OTHER: .40						
CHECK APPROPRIATE BOX(ES) <table style="width: 100%; border: none;"> <tr> <td><input type="checkbox"/> (a) HUMAN SUBJECTS</td> <td><input checked="" type="checkbox"/> (b) HUMAN TISSUES</td> <td><input type="checkbox"/> (c) NEITHER</td> </tr> <tr> <td colspan="3"> <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </td> </tr> </table>			<input type="checkbox"/> (a) HUMAN SUBJECTS	<input checked="" type="checkbox"/> (b) HUMAN TISSUES	<input type="checkbox"/> (c) NEITHER	<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
<input type="checkbox"/> (a) HUMAN SUBJECTS	<input checked="" type="checkbox"/> (b) HUMAN TISSUES	<input type="checkbox"/> (c) NEITHER						
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) <p>The book, <u>The Head of the Human Infant</u>, has been submitted to a publisher, the Johns Hopkins University Press. The Press has submitted a grant application to NIH-NLM for partial subvention sponsorship.</p>								

Project Description

I. Objectives

To provide a base of descriptive anatomy of the human infant and child for studies of normal development and for the definition of malformations.

II. Methods

Routines of dissection and illustration which are standard in the field of anatomy, supplemented by specialized radiography.

III. Major Findings

A general anatomy book. The Head of the Human Infant, has been completed in critic's draft. The book includes 840 manuscript pages and 425 illustrations of drawings of progressive dissections or successive sections of head of the newborn infant, or fetus near term; the brain is excluded. Separate Parts are under critical review by selected anatomists or pediatric surgeons having particular competence in anatomy.

This manuscript is accepted for publication by the Johns Hopkins University Press. The Press has submitted application to the National Library of Medicine for publication subvention.

IV. Significance

These studies provide information for description of normal development of anatomical form and structure. Such information is requisite for description of abnormalities of development, including those originating in the peripheral structures and those which evolve secondarily in these structures as effects of central neurological disease.

V. Proposed Course

Publication Prospectus of a book, The Head of the Human Infant, (see above)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00181-06 CI												
PERIOD COVERED October 1, 1980 - September 30, 1981														
TITLE OF PROJECT (80 characters or less) Postnatal Development of the Rat Skull														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Bosma, J. F.</td> <td style="width: 33%;">Chief, Oral Pharyn Dev Sec</td> <td style="width: 33%;">NIDR DS</td> </tr> <tr> <td>Murayama, D.</td> <td>Illustrator</td> <td>NIDR DS</td> </tr> <tr> <td>Sapperstein, S.</td> <td>Secretary</td> <td>NIDR DS</td> </tr> <tr> <td>Koback, A.</td> <td>Secretary</td> <td>NIDR DS</td> </tr> </table>			Bosma, J. F.	Chief, Oral Pharyn Dev Sec	NIDR DS	Murayama, D.	Illustrator	NIDR DS	Sapperstein, S.	Secretary	NIDR DS	Koback, A.	Secretary	NIDR DS
Bosma, J. F.	Chief, Oral Pharyn Dev Sec	NIDR DS												
Murayama, D.	Illustrator	NIDR DS												
Sapperstein, S.	Secretary	NIDR DS												
Koback, A.	Secretary	NIDR DS												
COOPERATING UNITS (if any) National Library of Medicine Philadelphia Children's Hospital University of Michigan														
LAB/BRANCH Diagnostic Systems Branch														
SECTION Oral and Pharyngeal Development														
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205														
TOTAL MANYEARS: .85	PROFESSIONAL: .10	OTHER: .75												
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) A PHS-NLM Grant Application for subvention of publication of the book, Postnatal Development of the Rat Skull has been approved at a high priority score. The monies of the publication subvention have been received by the University of Michigan. The book is now at the University of Michigan Press. Copy editing is completed. The authors are awaiting galley proofs.														

Project Description

I. Objectives

Normative demonstration of postnatal development of the individual bones and teeth and of the cranial composite and mandible in the rat.

II. Methods

Of Part 1. Rat skulls of days 1, 15 and 60 were dissected after papainization. The individual bones were then photographed and drawn.

Of Part 2. Rats at 8 postnatal ages were injected alternately with Alizarin Red S or Alizarin Blue BB and sacrificed at intervals after last injection. Defleshed crania and mandibles were mounted in Bioplast and sawn in sections. Patterns of development in separate areas of each bone and tooth and of development of composites of related bones and teeth were worked out by comparison study of specimens stained on various calenders.

III. Major Findings

Normative illustrations are prepared in the cranium and its bones and of the mandible. These constitute the basis of a textual description of the postnatal development of the rat skull on an individual bone and a regional basis.

The patterns of apposition and resorption at the margin and in the interior of the various portions of individual bones and teeth have been defined and further illustrated by schematics. The study materiel of Part 2 as prepared for publication, combines color photographs (in 120 projection slides) with tracings of the corresponding anatomical transsections. Each of these atlas units includes a projection slide, derived illustrations and textual commentary.

This volume also includes a review of vital marking of skeleton by alizarin and other stains which are chemically incorporated into ossifying tissues.

IV. Significance

This is the first comprehensive description of skull development of a laboratory mammal in this extent of age range, in this inclusion of entire skull and all teeth, and in this extent of detail. The descriptions and associated interpretations are significant contributions to information and understanding of normal mammalian development. And they are of normative value in definition of variations of rat skull and tooth development.

V. Proposed Course

Publication of the book, Postnatal Development of the Rat Skull by the University of Michigan Press, under subvention provided by NIH-NLM Grant Application, 1-R01 LM03464-01. The authors are now awaiting galley proofs.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER 201 DE 00182-06 CI												
PERIOD COVERED October 1, 1980 - September 30, 1981														
TITLE OF PROJECT (80 characters or less) Studies of Sensorimotor Impairments of the Mouth and Pharynx														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Bosma, J. F.</td> <td style="width: 33%;">Chief, Oral Pharynx Dev Sec</td> <td style="width: 33%;">NIDR DS</td> </tr> <tr> <td>Murayama, D.</td> <td>Illustrator</td> <td>NIDR DS</td> </tr> <tr> <td>Sapperstein, S.</td> <td>Secretary</td> <td>NIDR DS</td> </tr> <tr> <td>Koback, A.</td> <td>Secretary</td> <td>NIDR DS</td> </tr> </table>			Bosma, J. F.	Chief, Oral Pharynx Dev Sec	NIDR DS	Murayama, D.	Illustrator	NIDR DS	Sapperstein, S.	Secretary	NIDR DS	Koback, A.	Secretary	NIDR DS
Bosma, J. F.	Chief, Oral Pharynx Dev Sec	NIDR DS												
Murayama, D.	Illustrator	NIDR DS												
Sapperstein, S.	Secretary	NIDR DS												
Koback, A.	Secretary	NIDR DS												
COOPERATING UNITS (if any) Johns Hopkins Medical Center; Clinical Center, NIH; NICHD, NIH; NINCDS, NIH														
LAB/BRANCH Diagnostic Systems Branch														
SECTION Oral and Pharyngeal Development Section														
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205														
TOTAL MANYEARS: .85	PROFESSIONAL: .50	OTHER: .35												
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords) Patients with motor and/or sensory <u>impairments</u> of <u>feeding</u> or of speech or other upper respiratory performances, either of malformation, of inflammatory or neurological disease or following <u>cancer surgery</u> , are studied by <u>sensory testing</u> , cinephotography, cineradiography and speech analysis.														

Project Description

I. Objectives

Anatomical abnormalities and performance impairments of the pharynx, mouth and/or larynx may result from various disorders, including:

- malformation
- neoplasia and related surgical excision and other modifications
- peripheral sensory and/or motor disorders
- abnormalities of brain representations of the pharynx, mouth and larynx, or of their performances

These studies are designed to describe and define these anatomical abnormalities and their physiological correlates, and for the purpose of devising and applying therapies for disabilities of feeding and of speech and other respiratory functions.

A continuing limitation in the clinical evaluation and care of persons who have abnormalities and performance impairments of the pharynx, mouth and larynx is that the methods of demonstration, evaluation and therapy are dispersed among various clinical specialties. Within the year of this Report a multi-specialty group (radiology, otolaryngology, gastroenterology, neurology and rehabilitation medicine) has been organized for the clinical care of these persons at the Johns Hopkins Hospital, in collaboration with NIH.

II. Methods

Standard procedures of cineradiography and cinephotography are employed, as well as manometric and other physiological recordings. The regional performances of feeding, speech and other respiratory actions are described in infants, children and adults. Selected patients having sensory disorders of the oral and pharyngeal regions are further evaluated by sensory testing. Patients who have surgical excision for cancer are studied as examples of the modification of sensory input by ablation.

III. Major Findings

This Hopkins-NIH multispecialty group has substantially extended its method adaptations and derived insights and therapies. Certain advances are mentionable:

1. Recognition of the importance of adequate oral food preparation and of adequate control of the junction of the mouth and pharynx upon the competence of pharyngeal swallow.

2. Increased recognition of the role of the senses in feeding, specifically in pertinence to oral preparation of food, to control of the junction of the mouth and pharynx, to adequate emptying of the pharynx during swallow, and to adequate closure of the palatopharyngeal isthmus and of the larynx during swallow.
3. Studies of the interactions of swallow and respiration of impaired persons have led to more specific and meaningful categorization of laryngeal penetration of pharyngeal content: whether such penetration is prior to swallow, during swallow, or of unswallowed bolus after swallow.
4. Recognition of the importance of the physical character of the ingesta in the feeding of orally and/or pharygeally impaired persons. Impaired persons have been fed ingesta of differing physical consistency while under radiographic observations. By this means, ingesta of optimal consistency have been identified. By corresponding adaptation of ingesta, it has been possible to maintain certain impaired patients in adequate hydration and nutrition without the otherwise expected resort to feeding by nasogastric tube or by gastrostoma.

IV. Significance

Adaptation of selected diagnostic methods, including sensory evaluation, motion recording radiography and other methods have enhanced the definition of sensorimotor disorders of the mouth, pharynx and larynx. This has contributed to the recognition of related elements of separate disorders, to anticipation of some impairments in progressive diseases, and to therapy of disorders which are shown to have common pathogenic mechanisms.

V. Proposed Course

Participation of J. Bosma in the specialty composite of the Hopkins group will be increased during the pending year. Significant advances in the evaluation, diagnosis and care of orally and pharyngeally impaired persons may be anticipated as a result of combination of the resources of the Clinical Center with those of the Johns Hopkins Medical Institutions.

The observations and interpretations developed by the group are being presented at national and international meetings of specialty societies and corresponding publications in specialty journals are pending. A major effort is the preparation of a volume, Radiography of the Pharynx, under authorship of James F. Bosma and Martin Donner, of the Department of Radiology, the Johns Hopkins Medical Center. Publication will be by Springer-Verlag.

Publications: Bosma, J.F. and Henkin, R.I., Hypoplasia of the Nose and Eyes, Hyposmia, Hypogeusia and Hypogonadotrophic Hypogonadism in Two Males, J. Craniofac. Genet. Devel. Biol., 1: June, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00212-05 CI									
PERIOD COVERED October 1, 1980 - September 30, 1981											
TITLE OF PROJECT (80 characters or less) Taste and Its Disorders											
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 35%;">Weiffenbach, J. M.</td> <td style="width: 35%;">Research Psychologist</td> <td style="width: 30%;">NIDR DS</td> </tr> <tr> <td>Cowart, B. J.</td> <td>Psychologist</td> <td>NIDR DS</td> </tr> <tr> <td>Taylor, R. L.</td> <td>Student Trainee (Behav Sci)</td> <td>NIDR CI</td> </tr> </table>			Weiffenbach, J. M.	Research Psychologist	NIDR DS	Cowart, B. J.	Psychologist	NIDR DS	Taylor, R. L.	Student Trainee (Behav Sci)	NIDR CI
Weiffenbach, J. M.	Research Psychologist	NIDR DS									
Cowart, B. J.	Psychologist	NIDR DS									
Taylor, R. L.	Student Trainee (Behav Sci)	NIDR CI									
COOPERATING UNITS (if any) NIA, NIH NCI, NIH											
LAB/BRANCH Diagnostic Systems Branch											
SECTION Oral and Pharyngeal Development Section											
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205											
TOTAL MANYEARS: 2.50	PROFESSIONAL: 1.00	OTHER: 1.50									
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS											
SUMMARY OF WORK (200 words or less - underline keywords) The selection and refinement of appropriate <u>psychophysical methods</u> for the separate measurement of the various aspects of <u>taste perception</u> is a primary and continuing concern of this project. Normal variation in taste perception with chronological <u>age</u> is investigated with procedures which quantify not only the taste detection threshold but also the intensity and pleasantness of the taste experience elicited by stimuli at more commonly encountered intensity levels. Naturally occurring anomalies and therapeutically induced changes in taste are similarly investigated.											

Project Description

I. Objectives

This project employs selected modern psychophysical methods to define the relation of taste perception to age and experience, to saliva and to oral or systemic disease. Patients presenting with disorders of taste perception as the primary symptom are also studied. Current measurement techniques are examined in relation to their statistical base and the advances made by investigators of other sensory systems.

II. Methods

Currently, all testing is done with room temperature tastant fluids and an immediately prior rinse of double-distilled water. For threshold measurement, the "up-down" procedure for determining stimulus strength is combined with a forced-choice response format. Variation of procedure within this class of methods is studied by computer simulation. Measures of the intensity and pleasantness of supra-threshold stimulation are obtained by direct scaling using cross-modality matching to linear extent.

III. Major Findings

Detection thresholds and direct scaling have been obtained in a collaborative investigation of the development of taste perception with the National Institute of Aging (NIA). Subjects range in age from the early twenties to the late eighties. The thresholds obtained for sodium chloride increased with age in excellent agreement with the data obtained by others. Quinine sulfate thresholds were significantly related to age but did not show age group differences by analysis of variance. No significant age-related threshold changes were demonstrated for citric acid or sucrose. Thus, detection thresholds for the four taste qualities undergo quite different changes with age. Significant effects for two of the four taste qualities were revealed when the slopes of the intensity function for individual subjects were analyzed by separate age vs sex analyses of variance. For quinine, a main effect reflects a flattening of slope with aging. For sodium chloride, an interaction reflects a decline in slope with age for women accompanied by a significant steepening of the slope for men.

Detection thresholds for solutions representing each of the four basic taste qualities decreased approximately one and a half log units as a function of a four-fold increase in stimulus volume. The slope of the regression of threshold upon stimulus volume for substances representing the four taste qualities do not differ from each other. These parallel changes in threshold contrast with quality-specific changes observed by others who manipulated the effectiveness of the stimulus by altering its size or location within the oral cavity.

The Collings procedure for measuring taste recognition thresholds was examined in relation to response preference bias. Under the Collings procedure, subjects are required to respond with a taste quality name to each test stimulus. The responses given by subjects when they are unable to correctly identify the stimulus are not an unbiased selection from among the four response alternatives. On their initial exposure to this procedure, from one quarter to one third of the subjects from each of three groups displayed disproportionate selection of responses significant at beyond the .05 level. When a dozen of the subjects were retested on a subsequent day the number of them displaying significantly disproportionate responding increased. When data from day one and two are combined 8 of 12 subjects showed significant departures from chance expectation. The Collings method, unlike the standard forced choice procedure it resembles, contains no mechanism for insulating measured thresholds from the effects of response bias. The use of this popular and otherwise attractive method is strongly discouraged.

A computer program providing a generalized simulation of the family of tracking procedures used by psychophysicists to adjust the strength of test stimuli on successive trials during threshold measurement has been developed with L. Gray from the University of Virginia Medical Center. It has demonstrated that, in the absence of stimulus input, a tracking rule that increases the strength of the stimulus after each error and decreases it after each correct response yields a simulated threshold at its starting point. In contrast, if a repetition of the stimulus after an initial correct response is required and both must elicit correct responses before the strength is decreased. The value of the test stimulus is forced upward away from the starting point. A detailed study of the implications of these findings was carried out with human subjects. It defines the degree to which our standard procedure protects against the effects of inappropriately low starting points.

IV. Significance

The human taste system is a major oral sensory system. Through its role in the control of ingestion, taste affects both systemic nutrition and oral exposure to cariogenic substances. The taste system is liable to dysfunctions which are both debilitating and poorly understood. Variations in taste with systemic disease suggest that they may serve as diagnostic indicators.

Saliva plays a major role in taste function. Saliva contents, whether glandular excretory product or exudate, modify the taste experience. Taste threshold testing can assess the taste experience either with saliva or without saliva. The latter assesses the base function of the taste apparatus; the former its in vivo performance.

V. Proposed Course

Most studies of this project are either complete or nearly so. The study of metallic taste generated by elevated (100 millivolt) potentials between restorations of dissimilar metals will be completed as part of project Z01 DE 00217 - 03 LBS. The collaboration with NIA investigators at the Gerontology Research Center in Baltimore on longitudinal studies of taste and aging continues and protocol changes for the next cycle of the study are in design.

Publications

Wolf, R.O. and Weiffenbach, J.M.: Saliva and taste disorders.
In T. Zellars Advances in Physiological Science,
Vol. 28 Saliva and Salivaiton, Akademiai Kiado,
Budapest, Hungary and Academic Press, 1981.

Cowart, B.J. Development of taste perception in humans; Sensitivity and preferenc throughout the life span. Psychological Bulletin, 90 (4);43-73, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00065-10 CI
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Development of Evaluation of Improved Dental Radiographic Systems with Emphasis on Factors Influencing Diagnostic Performance		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Webber, R.L. Grondahl, H.G. Grondahl, K. Okano, R. Ruttimann, U. Dwyer, A.	Dental Director Visiting Scientist Visiting Fellow Visiting Fellow Sr. Staff Fellow Staff Radiologist	NIDR DS NIDR DS NIDR DS NIDR DS NIDR DS CC DRD
COOPERATING UNITS (if any) Clinical Dental Services Section, NIDR; NIDR Extramural Restorative Materials Program; Division of Electronic Products, Bureau of Radiological Health; X ray Physics Group, National Bureau of Standards		
LAB/BRANCH Diagnostic Systems Branch		
SECTION Diagnostic Methodology Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland		
TOTAL MANYEARS: 3.30	PROFESSIONAL: 2.02	OTHER: 1.28
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Factors influencing the <u>clinical per-</u> <u>formance of x-ray systems</u> both dental and medical are being modeled and evalu- ated in vitro using <u>computer simulations</u> and quantitative measurements derived from radiographic phantoms. The effects of continuous probability density functions on diagnostic systems are being explored theoretically using a Bayesian approach. When applied to quantum-limited x-ray systems it is possible to express information transfer vs. x-ray modulation and photon fluence for a variety of radiographic systems of biomedical interest. Of particular concern is the relative influence of continuous measures of prior information. The effect of extraneous x-ray scatter on photon statistics and radiographic contrast has been assessed as has been the role played by variations in spectral sensitivity and nonlinear contrast gain associated with common film-screen systems. Comparable work on non-screen film systems largely has been completed which confirms previous statements regarding the projected impact of exposure reduction on diagnostic performance.		

Project Description

I. Objectives

The purpose of this project is to study existing and new radiographic systems through in vitro modelling, and the development of prototypes suitable for clinical evaluation. Much of the effort is concerned with determining the limits imposed by ideal systems in order to assess rationally, relative efficiency measured in terms of dose, turn-around time, and diagnostic accuracy.

II. Methods and Major Findings

Promising x-ray sources and image-detector configurations are being studied in collaboration with other government agencies and private interests. Much of the work involves computer simulation coupled with clinically meaningful, in vitro measurements in order to rationally relate system elements to the diagnostic task to be accomplished.

The rationale underlying the selection of pertinent elements for investigation is based on general consideration of complete diagnostic systems. Within this context it is possible to classify limiting factors with regard to where in the process of data transfer, the desired information is lost. This project emphasizes factors which are determined either by the diagnostic sampling strategy, or by the amount of information reaching the interpreter.

Studies of a sample-limited system include measuring the effect of exposure geometry on diagnostic performance obtainable from dental radiographs. Results based on a mixed, components-of-variance model suggest that changes in beam angulation of as little as 2.5 degrees have the same impact on the observed standard deviation of picture elements in the difference image as changes in film exposure of 75 %, irrespective of the anatomical region exposed. These findings confirm previous observations that factors other than information-capacity limit the detectability of radiologic changes of dental interest.

The study of capacity-limited systems currently involves analyses of continuous probability density functions using a Bayesian approach. The basic idea is to extend the domain of signal-detection theory to permit rigorous description of continuous signal and noise distributions, within the context of information theory, as applied to quantum-limited systems. By considering Poisson distributed, random photon events as discrete decision outcomes associated with the output of an x-ray beam modulated by a continuously variable range of tissues having known attenuations, it is possible to compute a surface which determines the amount of diagnostic information transferred as a function of differences in tissue attenuation and photon fluence reaching an ideal detector. The analysis takes into account the prior probability of tissue differences, and thus permits lesion prevalence to be considered explicitly when assessing system performance.

A more applied study of a capacity-limited system involves a components-of-variance analysis of endodontic radiographs produced under conditions which control the system modulation transfer function (MTF) and vary the number of noise-equivalent quanta (NEQ) per unit area required to produce an image having an optical density of one. This work is being done in collaboration with the Division of Electronic Products, Bureau of Radiological Health.

The data indicate that the ability of a dentist to precisely measure the length of a # 15 file in the root canal, relative to the tooth apex, is relatively insensitive to quantum noise as measured by NEQ varying over a hundred-fold change

in x-ray exposure. The effects of changes in noise were more apparent in observers' ability to precisely identify the end of the endodontic file than in their ability to locate the associated tooth apex. This suggests that the smaller area of the file tip when compared with the tooth apex limits detectability in accord with the classic signal-detection theory. These data confirm the preliminary findings reported last year and further suggest a hypothesis suitable for future investigations based on the relation between NEQ and the observed standard deviation of the file and apex measurements.

Efforts continue to develop more efficient x-ray systems which facilitate serial analysis and display of diagnostic information. This work is being done in collaboration with the X-ray Physics Group at the National Bureau of Standards with support from a recently awarded NIDR Interagency Agreement administered through the extramural program. The proposed research involves experiments designed to select among several promising configurations of x-ray sources and high-efficiency detectors, and subsequent development of a working prototype system which will facilitate task-dependent control of both exposure geometry and radiation exposure.

III. Significance

Much of the work described in preliminary findings last year has been pursued further with the aid of controlled studies to provide statistically meaningful bases for generalization. For the most part the conclusions remain unchanged. They confirm that factors other than information capacity limit diagnostic performance obtainable from both ideal and existing system components for a variety of specific diagnostic tasks. Of particular importance are factors such as exposure geometry and mode of display which determine how diagnostic information is sampled and interpreted respectively. Unlike signal-to-noise ratio these factors are not limited by photon fluence so that there is room for substantial improvement in diagnostic performance without a concomitant increase in exposure to ionizing radiation. A notable exception was the observation that differences in x-ray beam-projection angles, which appear to be too small to contribute significantly to interproximal overlapping of adjacent crowns, do likely contribute a relatively large component to the total variance observed between successively obtained projections of the same dental region. This suggests that control of exposure geometry may be even more important than anticipated from previous experiments.

V. Proposed course.

Continued work in this area will emphasize methodological research directed toward specific clinical applications. Of particular interest is early detection of incipient lesions. To this end we shall look for ways to reduce accessible sources of diagnostic variation, and also will begin to consider other non-invasive techniques as bases for even earlier prediction of dental diseases which can be now traced radiographically.

Publications:

Webber, R.L.: "On Modeling Dental Radiographic Systems." Proceedings of the Bureau of Radiological Health Symposium on Biological Effects and Dosimetry of Ionizing Radiation, June, 1979. NIH Publication No. 80-1954, pp 219-227, September 1979.

Webber, R.L.: "Simulating the Effects of System Components on the Appearance of Dental X-Ray Images". Oral Surg., Oral Med., Oral Path. Vol. 51, No. 5, pp 560-565, May, 1981.

Webber, R.L.: "Toward a Better Understanding of Radiographic Contrast".
(In press)

Duckworth, J.E., Webber, R.L., Youmans, H., and Fewell, T.R.: "The Effects
of Spectral Distribution on X-ray Image Quality". (In press)

Okano, T., Grondahl, H.G., Grondahl, K., and Webber, R.L.: "Effect of Quantum
Noise on the Detection of Incipient Proximal Caries". (In press)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00158-07 CI
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) <u>Cephalometric Description of Growth Processes Through the Use of</u> <u>Symmetric Axis Coding</u>		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Webber, R.L.	Dental Director	NIDR DS
Blum, H.	Gen Physical Scientist	NIDR CR
Grondahl, K.	Visiting Fellow	NIDR DS
COOPERATING UNITS (if any) DCRT, NIH		
LAB/BRANCH Diagnostic Systems Branch		
SECTION Diagnostic Methodology Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland		
TOTAL MANYEARS: 0.95	PROFESSIONAL: .40	OTHER: .55
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The <u>symmetric-axis transformation</u> of Blum is being applied to computer-abstracted chronological tracings of lateral <u>cephalograms</u> produced from normal <u>mandibuli</u> . Specific parameters conveniently obtained from the transformed <u>boundary description</u> are being tallied both within and between individuals as a function of time in order to more rigorously test the observed bases for <u>morphological invariance</u> described previously. These parameters include the <u>limiting angles</u> determined by the ramus branch-point, axis-segment lengths, radius functions at points of maximum or minimum width, axis curvature, and homologous ratios of related measures. Preliminary data are consistent with previous observations and suggest further that specific ratios may permit statistically meaningful discrimination of in- dividuals in ways which are relatively independent of age. Future plans for extension of this work will depend heavily on the results of rigorous statistical analysis, and the ability to find applications of specific interest to research collaborators.		

Project Description

I. Objectives

Previous efforts to characterize the shape of biological structures with the aid of the symmetric-axis geometry of Blum are being extended to provide rigorous bases for statistical analysis of selected cephalometric data. The goal is to apply this method to specific data in an effort to unequivocally demonstrate its diagnostic utility as a morphometric tool in a specific application.

II. Methods

A series of computer abstracted tracings of normal cephalograms obtained from a data base made available by the Center for Human Growth and Development, the University of Michigan, are processed to yield symmetric-axis transformations of lateral projections of the mandibular border. Special programs are then written to abstract out promising, symmetric-axis based, parameters for longitudinal comparison both within and between radiographed individuals.

Parameters studied include limiting angles determined by branch-points in homologous portions of the symmetric-axis, axis-segment lengths, radius functions at points of maximum or minimum width, axis curvature, and homologous ratios of related measures. Particular emphasis is being placed on triple-point angles in the condyle because of the apparent relative stability over time noted previously. This work is being done in collaboration with the Laboratory of Statistical and Mathematical Methodology, DCRT.

III. Major findings

The data have only recently been abstracted and are currently being analyzed statistically. Preliminary observations based on selected measurements suggest that ratios may be relatively independent of age and yet vary significantly between individuals, however, the degree to which such observations can be generalized is still to be determined.

Other work has shown that the relative stability of the symmetric-axis triple-point angles reported previously in the region of the upper ramus is statistically significant assuming the underlying angles to be determined randomly using a model based on the Dirichlet distribution. However, the biological significance of this observation may be limited by the constraining effect of observed ramus widths, in the region of the triple-point, on the domain of possible triple-point angles. The problem is complicated by the intrinsic inaccuracy of the tracings which precludes meaningful estimates of boundary curvature at specific points, irrespective of the size of the digitization matrix.

V. Proposed course

Future plans in this area will depend heavily on the degree to which the data converge statistically, and collaborative interest by developmental biologists can be mobilized. Priority shifts away from geometry-based analyses and more toward medical-applications research by the Laboratory of Statistical and Mathematical Methodology, DCRT, coupled with our own plans to focus more intensely on specific diagnostic problems pertinent to caries and periodontal disease, will likely curtail the degree to which this work can be pursued in the future.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00211-05 CI																								
PERIOD COVERED October 1, 1980 to September 30, 1981																										
TITLE OF PROJECT (80 characters or less) Enhancement of Diagnostic Images																										
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT																										
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Webber, R.L.</td> <td style="width: 33%;">Dental Director</td> <td style="width: 15%;">NIDR</td> <td style="width: 19%;">DS</td> </tr> <tr> <td>Grondahl, H.G.</td> <td>Visiting Scientist</td> <td>NIDR</td> <td>DS</td> </tr> <tr> <td>Ruttimann, U.</td> <td>Sr. Staff Fellow</td> <td>NIDR</td> <td>DS</td> </tr> <tr> <td>Grondahl, K.</td> <td>Visiting Fellow</td> <td>NIDR</td> <td>DS</td> </tr> <tr> <td>Okano, R.</td> <td>Visiting Fellow</td> <td>NIDR</td> <td>DS</td> </tr> <tr> <td>Dwyer, A.</td> <td>Staff Radiologist</td> <td>CC</td> <td>DRD</td> </tr> </table>			Webber, R.L.	Dental Director	NIDR	DS	Grondahl, H.G.	Visiting Scientist	NIDR	DS	Ruttimann, U.	Sr. Staff Fellow	NIDR	DS	Grondahl, K.	Visiting Fellow	NIDR	DS	Okano, R.	Visiting Fellow	NIDR	DS	Dwyer, A.	Staff Radiologist	CC	DRD
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SUMMARY OF WORK (200 words or less - underline keywords) This project is an extension of pre- vious work involving the creation, development and testing of <u>image processing</u> techniques designed to improve <u>diagnostic performance</u> . Recent work features subtraction of sequentially obtained dental radiographs with the aid of a digital computer. Algorithms which provide bases for quantitative evaluation of the effects of contrast changes and variation in projection geometry are being developed in order to facilitate rejection of method-specific artifacts. Data obtained from double-blind assessment of diagnostic performance show significant improvement over the status quo. Other work involves nonlinear enhancement of CT scans of normal livers containing induced radiolucencies resembling low-contrast, metastatic nodules. By coupling a nonlinear contrast enhancement technique with a simple uniform aperture image convolution, it was possible to achieve a modest increase in diagnostic performance obtained from experienced radiologists.																										

Project Description

1. Objectives

This project is concerned with continued study of factors underlying diagnostic performance obtainable from images, with emphasis on the effect of mode of display on performance by human interpreters. Previous work has shown that image processing can improve diagnostic performance obtainable from dental radiographs for specific tasks not limited by the information capacity of the system. This work also demonstrated that monocular cues to depth can be used meaningfully to augment perceptibility of complex images of diagnostic interest.

Current objectives are based on logical extensions of these findings with emphasis on performance testing of promising enhancement schemes.

II. Methods and Major Findings

The relative success of enhancement mechanisms based on selective elimination of image information known to be irrelevant to specific diagnostic tasks has lead to the concentration of Section efforts in this direction. In previous years investigations of this type were described within the context of systems development but the concomitant effects on image interpretability suggest that such research might be more properly classified as an extension of existing image-enhancement projects which necessarily involve some loss of information capacity.

By limiting consideration only to radiographic changes occurring in time, spatial registration and subtraction of sequentially-obtained, radiographs provide an unsurpassed method for eliminating irrelevant detail. Not only does this process reduce the information capacity required of the system used to display the result, it also facilitates diagnostic performance by simplifying the image to yield displays which are much easier to interpret.

Although subtraction radiography is not new, only recently have the potential advantages of the method become practical in dental research. Digital technology provides highly reproducible bases for correcting for system non-linearities which facilitate quantitative abstraction of sequentially obtained data. The relative spatial stability of the teeth and supporting bone render this approach particularly well-suited to dental diagnostic applications.

Studies are under way to determine the effect of image subtraction on the detectibility of known lesions both in vitro and in vivo. In the latter case verification is done retrospectively from known clinical consequences of untreated controls in existing periodontal investigations. This work is being done in collaboration with investigators at the School of Dentistry, Goteborg, Sweden, and the Department of Oral Biology, State University of New York at Buffalo.

Another investigation involves the role of contrast and spatial-frequency band-pass on the interpretability of nodular lesions. This work is an extension of that reported last year wherein the effects of context-dependent, contrast enhancement (histogram equalization) and low-pass filtration via uniform aperture convolution were determined from CT images of normal livers containing computer induced lesions. The results of a double-blind study confirm that a statistically significant improvement in diagnostic performance results from systematic processing of this type irrespective of the model used for quantification. Of particular interest is the observation that the time required to make the

associated diagnostic decisions as well as the usual measures of accuracy and reliability were significantly influenced by judicious processing of the CT images. This work is being done in collaboration with investigators in the Diagnostic Radiology Department, Clinical Center.

Planned efforts to investigate the impact of the pseudo-solid techniques described in previous years have been restricted by limitation of the current range of grey-levels which can be displayed with existing software. The ability of the human eye to discern contour changes is much more sensitive than its ability to distinguish adjacent grey-levels. As a result a pseudo-solid display of a smooth contour produced with 6 bit dynamic range resembles a grossly quantized two-dimensional histogram rather than the continuous surface it was intended to depict. Therefore, considerable effort has been expended this year to increase the dynamic range of all image processing soft-ware from 6 bits (64 grey-levels) to 8 bits (256 grey-levels).

A similar need has been recognized with regard to capabilities in implementation of existing spatial-frequency, filtering algorithms. Application of Fourier methods are currently being explored in this regard. This work is being done in collaboration with the Scientific Systems Section, NIDR.

III. Significance

This project specifically targets research priorities recommended at the Consensus Workshop on Dental Radiology recently sponsored by the National Center for Health Care Technology in collaboration with the Bureau of Radiological Health and NIDR. The focus on digital subtraction methods also reflects an increase in demand by many institutions and research groups concerned with dynamic changes in mineralization of teeth and supporting tissues based on demonstrations of technical feasibility reported last year. The clinical advantages of reliable assessment of radiologic changes over time follow from the observation that both caries and periodontal disease are characterized by insidious, asymptomatic onset with largely irreversible consequences when left untreated in the early stages. The results of recent studies in this area demonstrate that significant increases in diagnostic performance can be obtained in ways consistent with a reduction in the required exposure to ionizing radiation when compared to conventional radiographic methods.

V. Proposed course

Further activity will continue to emphasize formal evaluation of promising enhancement methods with emphasis on the detection of small radiologic changes of clinical interest over relatively short intervals of time.

Publications:

Grondahl, H.G., Grondahl, K., Okano, R., and Webber, R.L.: "Statistical Contrast Enhancement of Subtraction Images". (In press).

Grondahl, H.G., Grondahl, K., and Webber, R.L.: "A Digital Subtraction Technique for Dental Radiography". (In press).

Grondahl, H.G., and Grondahl, K.: "Subtraction Radiography for the Diagnosis of Periodontal Bone Lesions". (In press).

Grondahl, H.G., Grondahl, K., and Webber, R.L.: "Digital Subtraction Radiography for Diagnosis of Periodontal Bone Lesions with Simulated Fast Speed Systems". (In press).

ANNUAL REPORT OF THE
NEUROBIOLOGY AND ANESTHESIOLOGY BRANCH
NATIONAL INSTITUTE OF DENTAL RESEARCH

The Neurobiology and Anesthesiology Branch is concerned with the study of oral-facial sensation, with particular emphasis on mechanisms of pain and the development of new methods for controlling pain in humans. The Branch is composed of three sections that utilize anatomical, physiological, behavioral, pharmacological and psychophysical techniques to study neural function as it relates to the processing of sensory signals about the threat of tissue-damaging stimulation. The Neural Mechanisms Section includes the following research activities: 1) correlative morphological and physiological studies of the organization of the medullary and spinal dorsal horns and the response of specific neuronal cell types to innocuous and noxious stimuli; 2) correlative behavioral and physiological studies to determine the role of different peripheral and central neural populations in pain and temperature discrimination. The Neurocytology and Experimental Anatomy Section is concerned primarily with the study of the medullary and spinal dorsal horns utilizing light and electron microscopy and various tracer and marking methods for identifying putative neurotransmitters. The Clinical Pain Section develops new methods for measuring and assessing experimental and clinical pain and applies these methods to the study of various pharmacological and non-pharmacological techniques potentially useful in the control of anxiety, apprehension and pain associated with dental procedures and in the treatment of chronic pain.

There is extensive collaboration between investigators in the three research groups. Correlative studies on neuronal structure, chemical mediators and physiological properties are being carried out to elucidate in detail the circuitry of the medullary and spinal dorsal horns and their relationship to pain mechanisms. Studies of chronic pain in humans involve the use of behavioral and psychophysical techniques that also have been employed in correlative animal behavioral and physiological studies. The effects of intravenous sedative drugs are evaluated utilizing the improved psychophysical assessment methods of pain and anxiety developed by the pain measurement group. Finally, our previous animal research has provided the conceptual framework for present studies on the role of endogenous pain-suppressing mechanisms in postsurgical pain.

This year we have continued to develop our chronic pain research program in collaboration with consultants in neurology, neurosurgery, anesthesiology, psychology and psychiatry. Patients receive extensive observation of their pain problem within a research environment. They are admitted to the Clinical Center, NIH, for 1-3 week periods and participate in research studies in which their responses to experimental pain stimuli as well as their clinical pain are evaluated. This detailed experimental and clinical work-up forms the baseline for further evaluation of new pain control methods. We also have expanded our collaborative clinical pain research efforts with other Institutes and are initiating

studies on cancer pain, pain associated with diabetic neuropathies, and the evaluation of new pharmacological agents for the control of acute and chronic pain. We look forward to the completion of the Clinical Center Ambulatory Care Research Facility and the establishment of a multi-Institute research clinical pain program under our leadership.

Investigators in the Branch received numerous awards and honors this year. Dr. Ronald Dubner, Chief, Neurobiology and Anesthesiology Branch, received the 1981 Frederick Birnberg Research Medal from Columbia University on April 3. The award, sponsored by the University's School of Dental and Oral Surgery Alumni Association, was established to encourage dental research of excellence. It is awarded to individuals who have made outstanding contributions in dentistry through encouragement of research workers or through the presentation of their own research investigations. Members of the Branch were invited speakers at numerous workshops at the Third World Congress of the International Association for the Study of Pain, held in Edinburgh, Scotland. Invited presentations also were given at the annual meetings of the Society for Neuroscience and the International Association for Dental Research.

The research highlights of the Branch will be presented by topic rather than by Section, in view of the extensive interaction between the groups.

The Neural Circuitry of the Medullary and Spinal Dorsal Horns

The lower end of the spinal trigeminal nucleus in the brain-stem, called trigeminal nucleus caudalis, is directly continuous with the spinal dorsal horn and is homologous to it in terms of structure, chemistry and physiological function. For these reasons, it is more properly referred to as the medullary dorsal horn. This year we have continued our in-depth studies of the functional organization of the medullary and spinal dorsal horns and their role in pain mechanisms.

We have performed correlative anatomical and physiological studies of the intrinsic neurons of the spinal dorsal horn. The response properties of these neurons are determined electrophysiologically. The neurons are then impaled with fine micropipettes and horseradish peroxidase iontophoresed into the cell. This powerful technique reveals the location and configuration of the dendritic and axonal processes of individual physiologically-characterized cells. We have continued to examine the properties of the superficial layers of the dorsal horn as well as initiating studies on the organization of the deeper layers. Layers I and II contain identified neuronal cell types that respond exclusively to noxious stimuli (nociceptive-specific), respond to both innocuous and noxious stimuli (wide-dynamic-range) or respond only to innocuous stimuli (located in layer IIb only). These superficial layers also contain a wealth of chemical mediators that are released by primary afferent or descending neurons projecting to this region as well as by intrinsic

neurons. Using immunocytochemical techniques in combination with the intracellular horseradish peroxidase (HRP) method, at both light and electron microscopic levels, we are examining the role of these putative neurotransmitters in the neural circuitry of the superficial dorsal horn.

During this past year, the synaptic connections of a layer I smooth pyramid, a layer IV cell and several layer IIb islet cells that were intracellularly filled with HRP were examined at the electron microscope level. The layer I smooth pyramid did not contain synaptic vesicles in its dendrites and received numerous synapses on its cell body and dendrites from dome-shaped axonal endings that were identified as descending serotonergic endings in earlier studies. The cell also gave off axon collaterals whose endings synapsed on other layer I cell bodies and dendrites. If future studies indicate that such layer I neurons are enkephalinergic, a possible neural circuit for the interaction between serotonin and enkephalin in the dorsal horn would be identified.

The most impressive feature of the layer IV cell was its dorsally directed dendrites which entered layers I and II as well as Lissauer's tract. In these locations it received numerous synaptic contacts from small axonal endings which resembled dome-shaped, serotonergic endings but the dendrites of the cell did not enter synaptic glomeruli. These observations suggest that many of the neurons in the deeper laminae of the dorsal horn which send some of their dendrites dorsally into layers I and II may receive appreciable input from descending aminergic axons on these dorsal dendrites but very little input from the primary axons which arborize in these layers.

The IIb islet cells, like their counterparts in layer IIa studied previously, contain aggregates of synaptic vesicles in their dendrites and form dendrodendritic synapses on neighboring dendrites within and outside of glomeruli. The IIb islet cells also appear to contain enkephalin as a neurotransmitter. This identification was made by comparing the light and ultrastructural morphology of intracellularly stained layer IIb islet cells with that of immunocytochemically labeled ENK soma and dendrites in layer IIb. At the ultrastructural level the ENK labeled dendrites contain vesicles and received synapses from primary central endings in glomeruli, as do the layer IIb islet cells. This finding provides insight into the role of enkephalin in the modulation of sensory transmission at the spinal level.

In studies of the neural circuitry of the deeper layers of the dorsal horn, we have concentrated our efforts on two groups of neurons, the large layer IV cells that send their axons to the dorsal column nuclei via the dorsal columns (dorsal column postsynaptic tract), and the small interneurons of layer III. Retrograde HRP methods demonstrated that the dorsal column postsynaptic tract is a major system in the cat. Neuronal cell bodies were most numerous in a narrow band of about 115 μ m in layer IV throughout most of the dorsal horn. Estimates of cell

density were equivalent to published reports of the density of spinocervical tract neurons and about one-third the estimated density of spinothalamic tract neurons.

Electrophysiological studies of dorsal column postsynaptic tract neurons have shown that about one-half of these cells are innervated only by low threshold mechanoreceptive primary afferents. The other one-half are excited by low threshold mechanoreceptive primary afferents but these cells also respond with a maintained increased discharge frequency to noxious pinch (wide-dynamic-range type). Several of the dorsal column postsynaptic tract neurons were successfully impaled and intracellularly stained with HRP. Their perikarya were found throughout layer IV. Their dendritic arbors were elongated rostrocaudally, but relatively compressed mediolaterally. Although a few cells had apical dendrites that penetrated layer II, none of the cells had any appreciable amount of dendritic surface within layer II. The axons of two cells were very well stained and issued axon collaterals that coursed through layer IV and into layer V. Thus, at least some dorsal column postsynaptic neurons issue synapses into local neuronal circuits.

Using HRP and immunocytochemical methods, we have observed that layer III contains many small neurons with dendrites that travel mainly in the long axis of the spinal cord while sweeping dorsally. A few of these cells have distal dendrites within layer IIb, but most dendrites remain in layer III. In cases where axons were visualized, they often issued collaterals within layer III. These small layer III neurons contain enkephalin as determined by immunocytochemical methods. Several of these layer III neurons have been characterized electrophysiologically and intracellularly stained with HRP. They receive input from A-beta, low-threshold mechanoreceptive primary afferents innervating skin and guard hairs. These observations of a population of layer III interneurons that are excited by low intensity mechanical stimulation and that are immunoreactive for enkephalin suggest a possible functional circuit for the well known inhibitory effects that low threshold mechanoreceptor activation exerts on nociceptive dorsal horn neurons.

Combined retrograde HRP and immunocytochemical studies have revealed a third neural circuit involving enkephalin-containing neurons in the dorsal horn. Enkephalin immunoreactive axonal endings were shown to make direct synaptic contact with the soma and proximal dendrites of layer V dorsal horn thalamic projection neurons. This observation demonstrates that one major site of opiate modulation of the transfer of sensory information in the dorsal horn is a direct synaptic event on the projection neurons themselves. It also is the first direct anatomical demonstration of a synaptic relationship between axonal endings containing an opiate peptide and an identified postsynaptic neural element in the dorsal horn.

As a continuation of our earlier studies of monoamines in pain pathways, we have employed the immunocytochemical technique to localize

serotonin in the dorsal horn. The immunocytochemical approach has an advantage over the autoradiographic technique employed in previous studies of serotonin in that it allows visualization of the entire serotonin axon which can be followed as it courses through the neuropil. In preliminary observations, it appears that serotonin axons have a decidedly rostro-caudal orientation. Their numbers are greatest in layer I and decrease in layer IIa and are lowest in layer IIb. Serotonin also is present in other layers of the spinal cord. It appears that serotonin is found throughout the spinal cord with each layer varying only in the density of innervation. As in the tritiated serotonin uptake experiments, ultrastructurally, layer I and II serotonin axonal endings are mainly dome-shaped, forming a single synapse with dendritic shafts and spines.

The experiments described above have identified several important sites of action of neurotransmitters in the dorsal horn. The analysis of monoaminergic axonal endings is of particular significance since the activation of descending aminergic pathways are implicated in mechanisms of analgesia. The study of enkephalinergic neural circuitry furthers our understanding of the role of opiates in pain and other somatosensory pathways.

Another important question relating to neural circuitry in the dorsal horn concerns the identification of the termination sites of the many different kinds of primary neurons activated by innocuous and noxious stimulation. Those primary axons which terminate in layer I are especially important to our understanding of pain perception because the neurons in layer I are one of the two major groups of neurons in the dorsal horn which receive nociceptive inputs and convey these inputs to higher centers in the brain. In recent studies utilizing the HRP method, two morphologically distinct kinds of primary axons were discovered. One of these generates many ultrafine endings along unbranched, long rostro-caudally oriented, collaterals which arise from thin parent branches in Lissauer's tract. In view of these thin parent branches, these ultrafine primary axons are considered to be unmyelinated primary axons. The second kind of primary axon generates large caliber endings on branched collaterals. These arise from relatively thick parent branches in Lissauer's tract, and on the basis of their size are considered to be A-delta, myelinated primary axons. The scalloped endings of both kinds of primary axon lie in the interior of glomeruli where they form axodendritic synapses on small dendritic shafts and spines. It is at these synapses that these two kinds of primary axons are thought to transfer nociceptive and thermal inputs directly to the dendritic arbors of layer I neurons.

Studies of the termination sites of tooth pulp afferents were continued this year. Two major sites were identified. One consists of a long continuous column which extends from the main sensory nucleus at its rostral limit through subnuclei oralis and interpolaris into layer V in the medullary dorsal horn at its caudal limit. The second termination

site is found in the dorsomedial parts of layers I and IIa in the medullary dorsal horn.

One of the important findings of earlier tooth pulp studies was the observation that dendrites of many neurons in layers I and II in the medullary dorsal horn exhibit degenerative changes following the extirpation of tooth pulps. This past year a series of experiments was begun in order to examine in a more systematic way the effects of nerve injuries on primary neurons themselves and on the neurons in the dorsal horn that are linked to them synaptically. Following the application of HRP to the superficial radial nerve on one side which had been cut thirty days earlier, and to the same uncut control nerve on the other side, similar numbers of HRP-filled cell bodies were found in the C₆-C₈ dorsal root ganglia on both sides. In addition, the density and layer distribution of the terminal axonal projection was similar on both sides of the C₆-C₈ spinal cord segments. These findings suggest that few if any primary neurons die as a result of the injury. However, many of the primary endings in layers II and III show a severe loss of their agranular synaptic vesicles which suggests that neural transmission between the injured primary neurons and the dorsal horn neurons may be lacking or markedly reduced. Another important sign of the loss of neural transmission is the appearance of numerous small cavities in the dendrites of layers II and III neurons. These cavities are similar to those found following tooth pulp extirpation and indicate transsynaptic degeneration in these dorsal horn neurons.

Behavioral Correlates of Neural Function in the Medullary Dorsal Horn

We have extended our analysis of the neuronal properties of the medullary dorsal horn by correlating response characteristics with behavior in awake monkeys trained in sensory discrimination tasks. As mentioned above, two general classes of dorsal horn neurons (wide-dynamic-range and nociceptive-specific), studied in anesthetized animals, convey information related to pain. Our major objectives this year were, 1) to determine whether neurons with sensory-discriminative properties send axonal projections to the thalamus; 2) whether neurons with task-related responses described previously also projected to the thalamus; and 3) to develop a new task that required monkeys to discriminate between small differences in noxious or innocuous temperatures in order to successfully complete the task. The new thermal discrimination task requires that monkeys report which of two simultaneously-applied heat pulses is warmer. Two contact thermodes are positioned symmetrically on the monkey's face. The baseline temperature of the probes is 35°C. At the beginning of each trial a panel is illuminated. The monkey presses the illuminated panel and is presented simultaneous heat pulses, one on each probe. The rise-times of the heat pulses are identical, but the final temperatures differ. After a variable time the thermodes return to 35°C and two side panels are illuminated. The monkey receives a water reward for pressing within two seconds the left panel if the thermode on

the left side of the face was warmer or the right panel if the right thermode was warmer. This task provides a psychophysical measure to determine difference limens for thermal intensities in the innocuous and noxious ranges. It is especially useful for the study of thermally responsive neurons to determine which neurons show differential responses to the smallest thermal intensity differences discriminable by the monkey. Presently we are training two monkeys in this task and defining difference limens in the innocuous and noxious thermal ranges.

In detection tasks described previously, monkeys are trained to detect the termination of innocuous thermal stimuli (37° - 43° C) and the onset of noxious heat stimuli (45° - 49° C) applied to the face (thermal task). In a visual task, the same monkeys detect the onset of a visual stimulus while behaviorally irrelevant thermal stimuli are presented. Neuronal activity in the medullary dorsal horn is correlated with a number of behavioral events such as panel press, temperature onset, temperature termination, panel release and reinforcement delivery. Our results show that medullary dorsal horn neurons differ along two response dimensions: (1) sensory-discriminative properties in response to thermal and mechanical stimuli; and (2) task-related responses independent of stimulus parameters and motor activity. We have found that in awake monkeys, two types of neurons that project to the thalamus are responsive to noxious thermal stimuli: wide-dynamic-range (WDR) neurons, which respond differentially to innocuous and noxious mechanical stimuli, and nociceptive-specific (NS) neurons, which respond exclusively to intense or noxious stimuli. Thermal response thresholds range from 41° to 47° C, and stimulus-response functions are monotonic from threshold to 49° C. For both WDR and NS trigeminothalamic neurons, greater neuronal discharges are associated with shorter behavioral discrimination latencies. These data show that thermally sensitive WDR and NS neurons transmit information to the thalamus that correlates with the monkey's ability to discriminate noxious thermal stimuli. Therefore, these neurons appear to participate in neural mechanisms underlying the sensory-discriminative aspects of pain.

Previously, we have described responses of thermosensitive and mechanosensitive medullary dorsal horn neurons that are independent of stimulus modality or stimulus parameters. In the present project we investigated these task-related properties in more detail and identified at least one output pathway of these neurons. We identified several types of these task-related responses. Some cells discharge when the monkey initiates the trial. Others discharge at the signal for panel release, whether that signal is a temperature change or light onset. The most common pattern of task-related activity is a transient or sustained discharge at trial initiation and an additional burst discharge after the signal for panel release. Task-related responses occur only during performance of a task and are related to sensory events that lead to successful completion of the task. Such responses are not correlated with specific face, arm or hand movements. Some neurons with each pattern of task-related activity project to the thalamus. Neurons with

task-related activity may be providing a gain control mechanism for somatosensory information that the animal must use for successful completion of the task. Additionally, these responses may be involved in the transmission of behavioral information to motor cortex to facilitate appropriate goal-directed behavior.

These studies are important in determining the neurons critical for signalling the intensity of painful thermal stimuli and transmitting this information to levels of conscious sensation. By studying the monkey's behavioral responses within a task we also can assess the influence upon pain perception of such variables as behavioral significance and predictability of noxious thermal stimuli. Concurrently, we can study modulation in activity of neurons involved in the transmission of noxious information from the face. Our data show that the neural representation of oral-facial nociception can be influenced by environmental and behavioral factors at the earliest stage of central integration and that this modulatory information is relayed to a thalamic nucleus that receives thermal sensory information. This work is a behavioral demonstration of non-pharmacological modulation of neurons involved in oral-facial nociception, and consequently is important in understanding non-pharmacological approaches to the control of oral-facial pain.

The Assessment of Experimental and Acute Clinical Pain

The purpose of these studies is 1) to develop psychophysical and behavioral models of pain perception that assess the intensity and unpleasantness of experimental and clinical pain sensation and also assess the ability of subjects to judge their perceptual experience, and 2) to use these models to assess the physiological and psychological mechanisms of pain and analgesia, and the efficacy of pharmacological and non-pharmacological methods of pain control.

We are continuing to study mechanisms of postoperative dental pain following the extraction of impacted third molars. Pain is assessed for one hour before and after intravenous injection of fentanyl, saline, or naloxone, or after no treatment, by visual analog and verbal descriptor scales of sensory intensity, unpleasantness and painfulness. Preliminary results show that the effect of saline placebo in reducing the magnitude of postoperative pain was significantly greater when the placebo was alternated double-blind with the administration of the narcotic fentanyl and no treatment than when it was alternated with only no treatment. This study also showed that naloxone did not produce hyperalgesia in comparison to placebo or no treatment. Previous studies suggest that naloxone reverses placebo-produced analgesia of postoperative dental pain. Our preliminary results do not support these previous findings that naloxone produces hyperalgesia in comparison to placebo, suggesting that endorphin mechanisms do not play a significant role in the effects of placebo drugs on dental postoperative pain. The finding that the placebo effect was altered significantly by experimental context emphasizes the role of psychological factors in placebo mechanisms.

A new study used an information-integration procedure called Functional Measurement to separately assess effects of intravenous medications on the perceptual, cognitive and response mechanisms involved in using a category scale to rate the subject's integrate of two stimuli, those evoked by electrical tooth pulp stimuli and those symbolized by a word. Results show that the narcotic fentanyl reduced the perceptual intensity of tooth pulp stimuli without altering the subject's ability to integrate or respond to the stimuli. The minor tranquilizer diazepam reduced the cognitive ability to integrate the stimuli without altering either the perception of the stimuli or the response to these perceptions. This model provides a method to distinguish between the effects of putative analgesic manipulations on pain perception, the verbal report of that perception, or the general ability to perform a pain rating and integrating task. These results suggest that this model may be useful in separating the physiological effect of a pain treatment from the psychological effects resulting from the experimental situation, expectations of the subjects, and the side effects of the treatment.

An additional study developed a new clinical pain scaling method, the descriptor differential scale (DDS) that applies techniques of experimental pain scaling to the assessment of clinical pain. This questionnaire provides 36 subscales anchored by verbal descriptors of sensory intensity, unpleasantness and painfulness, and requires subjects to rate their pain sensations on a 21-point scale in relation to each descriptor. This method anchors judgments to subjective standards and produces more data per observation than other methods, thereby reducing the variability of the resultant response measures. In addition, an analysis of the pattern of responses to the subscales yields a measure of scaling performance for individual subjects. Preliminary results show that the DDS is more sensitive than a visual analog scale in the assessment of placebo response to postoperative dental pain, and that it provides a sensitive measure of scaling ability.

In other studies in which new analgesic agents, such as flurbiprofen and etidocaine are being evaluated, new pain scales such as the DDS scale have been shown to have some advantages over traditional measures of analgesia. Where the difference between treatments is subtle, the DDS scale sometimes shows a significant difference, not detectable by other traditional analgesic scales. If replicated in other studies, the DDS scale may be an extremely useful tool for assessing new analgesic agents.

Assessment of Chronic Pain

We are continuing to evaluate the effects of narcotic analgesics and electrical brain stimulation on clinical and experimental pain in a group of chronic pain patients, some of whom received chronic brain electrode implants for pain relief. These electrodes are placed in brain pathways where they are presumed to activate descending, opiate-related, pain-suppressing systems. Although sixteen patients were

assessed this year, only three were considered candidates for electrode implants. Two have received implants but have not yet returned for evaluation. One patient receiving an electrode last year was reevaluated this year. Her pain appears to be controlled completely by infrequent stimulation and she presented with no pain on admission.

A related study compared the effects of morphine in normal pain-free subjects to the effects observed previously for chronic pain patients. Normal subjects scaled noxious thermal stimuli between 45° and 51° C presented to the volar surface of the forearm both before and after the double-blind administration of morphine or saline placebo. Following morphine administration, verbal descriptor responses of sensory intensity and unpleasantness were reduced in the normal subjects in comparison to placebo similar to previous findings in chronic pain patients. These results show that chronic pain patients and pain-free subjects both show decreases in sensory intensity and unpleasantness responses after morphine administration despite observed differences in pain thresholds and unpleasantness rating of thermal stimuli.

An additional study correlated experimental pain response with clinical pain response before and after morphine administration in a group of patients with chronic pain. Five drug-free patients assessed the sensory intensity and unpleasantness of thermocutaneous stimuli (46°-51° C) in separate sessions before and after the double-blind intravenous administration of morphine or saline placebo. Subjects also completed clinical pain questionnaires in each session. Morphine significantly reduced responses to both the experimentally induced pain sensations and the patient's clinical pain in comparison to placebo. This agreement between the clinical and experimental pain effects of morphine administration also support the validity of verbal scales of contact heat for the experimental assessment of pain control methods.

In other studies of chronic pain, we have continued to evaluate behavioral factors associated with the Myofascial Pain Dysfunction Syndrome (MPD). The illness behavior of MPD patients was compared with another group of patients with recurrent aphthous stomatitis. A questionnaire was used that evaluates the patients on a number of behaviors such as hypochondriasis, attitudes about the seriousness of their disease, and their perception of the psychological and somatic aspects of their illness. Both populations of patients scored similarly on all scales except on the scale indicating disease attitudes. It appears that MPD patients are less likely to accept that they do not have a serious illness despite reassurance from the clinician.

Control of Pain and Anxiety in Ambulatory Dental Patients

Investigations are being conducted on the analgesic properties of flurbiprofen, a new non-steroidal anti-inflammatory drug, and etidocaine, a long-lasting local anesthetic. These agents may be more useful in

controlling postsurgical dental pain than conventionally used drugs. A within-subject, double-blind crossover design is being employed in these investigations. Patients in need of bilateral extraction of impacted third molars serve as subjects. Subjects receive one of the two treatments on a random basis at the first appointment and the alternative treatment is administered at a second appointment, approximately two weeks later.

Preoperative administration of 50 mg of flurbiprofen was demonstrated to result in significantly less postoperative pain than 1000 mg of acetaminophen for all measures of analgesia employed. This represents a genuine therapeutic advantage in that no increase in side effects was noted. This study also demonstrated that the use of a within-subject crossover design is sufficiently sensitive to differentiate between active drugs in a sample as small as 20 subjects.

In a second analgesic study, preoperative and postoperative administration of 50 mg of flurbiprofen resulted in significantly less pain than postoperative administration of a commonly-used opioid-acetaminophen combination. In addition, the opioid combination tended to result in a higher incidence of side effects. In the second phase of this study, pre- and postoperative administration of 100 mg of flurbiprofen resulted in significantly less pain than did the opioid combination given on the same schedule. In both phases of this study patients expressed a clear preference for the flurbiprofen over the opioid combination.

Our preliminary results with the long-lasting local anesthetic indicate that etidocaine is suppressing pain during the first seven hours following surgery. In addition, the vast majority of patients evaluated to date indicated that, overall, they experienced less postoperative pain following etidocaine than following standard treatment.

The results of these studies suggest that both flurbiprofen and etidocaine are resulting in a significant reduction in postoperative pain when compared to standard treatment. These two treatments will be administered concurrently to determine if an additive effect can be seen on postoperative pain and to determine if the moderate to severe pain normally associated with painful dental therapy can be markedly reduced or eliminated.

In other studies we are evaluating the use of various medications for the relief of anxiety associated with dental procedures. Another objective of these studies is to assess the physiological and biochemical responses to the stress of surgery. Technological advances such as impedance cardiography and sensitive assays for epinephrine and norepinephrine permit a reexamination of the effect of surgical stress, exogenous epinephrine and their interaction with intravenous anti-anxiety drugs.

Studies conducted this year have demonstrated that epinephrine administered with local anesthetic results in a five-fold increase in

circulating epinephrine levels when compared to local anesthetic without epinephrine. Concomitant with this increase in circulating epinephrine levels is an increase in cardiac output, as measured by impedance cardiography, which is not seen in the group receiving local anesthetic without epinephrine. The stress of surgery was associated with increases in heart rate, systolic blood pressure and cardiac output. Premedication with diazepam did not attenuate the increased circulating epinephrine levels following local anesthesia or the increased cardiac output. Diazepam did prevent the stress-induced elevation in circulating norepinephrine levels seen in non-sedated patients, presumably by preventing sympathetic arousal.

These findings suggest that exogenously administered epinephrine with local anesthetic is being absorbed in sufficient amounts to result in measureable circulatory changes. While these changes are well-tolerated in healthy, young volunteers, they may not be so innocuous in the elderly or cardiovascular-risk patient. Because tens of thousands of local anesthetics are administered daily, it is worthwhile to examine this potential risk factor.

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00031-13 NA						
PERIOD COVERED October 1, 1980 to September 30, 1981								
TITLE OF PROJECT (80 characters or less) Design and Computer Interfacing of Neurophysiologic Instrumentation								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Brown, F.J.</td> <td style="width: 33%;">Electronic Engineer (Instru)</td> <td style="width: 33%;">NIDR NA</td> </tr> <tr> <td>Medlin, T.P.</td> <td>Supv. Computer Specialist</td> <td>NIDR OD</td> </tr> </table>			Brown, F.J.	Electronic Engineer (Instru)	NIDR NA	Medlin, T.P.	Supv. Computer Specialist	NIDR OD
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COOPERATING UNITS (if any)								
LAB/BRANCH Neurobiology and Anesthesiology Branch								
SECTION Neural Mechanisms Section								
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205								
TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:						
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SUMMARY OF WORK (200 words or less - underline keywords) This work involves the development of suitable <u>electronic</u> and <u>electro-</u> <u>mechanical instrumentation</u> to be used in neurophysiological, physiological and behavioral research. It involves the adaptation and interfacing of these and other instruments to a laboratory or <u>multipurpose computer</u> <u>installation</u> .								

1. Project Description

A DEC 11/34 computer, interfaced through an INTEL 80/10 micro-computer to control neurophysiological-behavioral experiments in one laboratory, has been interfaced through an INTEL 80/20 microcomputer to control similar experiments in a second laboratory. The second system has been designed to allow on-line acquisition and processing of stimulus and behavioral data as well as discriminated single cell neural data and one channel of electromyographic data. The INTEL 80/20 receives commands from the 11/34, controls stimuli, and time-stamps stimulus, neural, and behavioral events to an accuracy of one millisecond. The 80/20 also gathers rectified and averaged emg data every 8 milliseconds when desired, and buffers all data transfers to the 11/34 computer.

2. Publications:

None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00247-04 NA																		
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TITLE OF PROJECT (80 characters or less) Cytomorphology of functionally characterized spinal cord dorsal horn inter- neurons																				
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SUMMARY OF WORK (200 words or less - underline keywords) Neurons of the dorsal column postsynaptic tract (DCPST) were retrogradely labelled with HRP. Most cells were found in <u>lamina IV</u> . Counts of these neurons showed an average of <u>41.5 neurons</u> in each rostrocaudal millimeter of the dorsal horn. Antidromically identified and physiologically characterized DCPST neurons were intracellularly stained. Their dendritic arbors were rostrocaudally elongated (c. 1450 μ m) but relatively compressed mediolaterally (c. 450 μ m). Several cells were found to issue varicosity-bearing <u>axon collaterals</u> within and below their dendritic territories. Immunocytochemical studies revealed small interneurons in <u>lamina III</u> that were immunoreactive for <u>enkephalin</u> (ENK). Their perikarya were 10-15 μ m and their sparse dendritic arbors coursed rostro- caudally and dorsally. Neurons with apparently identical morphology were <u>intracellularly stained</u> with HRP. They all responded exclusively to activation of <u>low threshold mechanoreceptive</u> primary afferents with A beta axons. ENK neurons were found whose perikarya, proximal dendritic arbors, ultrastructure, and synaptic connectivity resembled <u>lamina IIb islet cells</u> .																				

1. Project Description:

Objectives: The spinal and medullary dorsal horns are the sites of the initial processing of information concerning tissue-damaging stimuli. The neural circuitry that processes this information, and subsequently transmits it to higher levels of the neuraxis, is poorly understood. Our objective has been to elucidate the function, structure, and neurochemistry of this circuitry. We have concentrated our efforts on two groups of neurons--the small interneurons of lamina III and the large lamina IV cells that send their axons to the dorsal column nuclei via the dorsal columns. We have, in addition, continued our work on the small interneurons in lamina II.

Methods Employed: We have used three different techniques in these studies:

1) Intracellular staining of physiologically characterized neurons:

The lumbosacral enlargements of anesthetized adult cats are prepared for electrophysiological recording in the usual manner. Single cell recordings are obtained with fine micropipettes that contain electrolytes and the enzyme horseradish peroxidase (HRP). The primary afferent innervation of the cell is characterized by applying a battery of natural stimuli (touch, hair displacement, pinch, noxious heat, etc.) to the cell's cutaneous receptive field (RF). Additional information is obtained by examining the conduction velocity and electrical threshold of activity evoked from percutaneous electrical stimulation of the RF. The cells are also characterized by their responses to selective electrical stimulation of the cervical dorsal columns (DC). Projection neurons whose axons ascend in the DC are identified by the presence of antidromic impulses. Following the physiological characterization we attempt to impale the cell. When the impalement is successful we inject HRP into the cell. After sacrificing the animal and sectioning the spinal cord we develop the electron- and optically-opaque HRP reaction product with the diaminobenzidine procedure. Successfully stained cells are examined microscopically and drawn.

2) Neuronal staining with retrogradely transported HRP:

In order to enumerate and to determine the position of the neurons that form the dorsal column postsynaptic tract (i.e., DCPST neurons), we made discrete partial transections of the dorsal columns at thoracic or cervical levels. A small piece of polyacrylamide gel that contained 15% HRP was placed into the transection. This gel releases HRP slowly and continuously; it has the additional advantage of restricting the spread of HRP. After survival periods of 24-48 hrs the cats are overdosed, perfused and the lumbosacral enlargement is sectioned serially in the sagittal plane. The retrogradely transported HRP is visualized with either diaminobenzidine or tetramethylbenzidine as the chromagen.

3) Immunocytochemical staining of enkephalinergic neurons:

We have used a commercially available antiserum raised against leucine enkephalin conjugated to bovine serum albumin. Based on radio-immunoassay data this antiserum has about 30% cross-reactivity to methionine enkephalin. Cross-reactivity to dynorphin has not been examined but practically no cross-reactivity has been found to any other known endorphin and no appreciable cross-reactivity exists for any of the other neuropeptides that are known to exist in the dorsal horn.

In order to increase the concentration of enkephalin immunoreactivity (hereafter designated ENK) within neuronal perikarya we pre-treat our cats with colchicine. Colchicine disrupts axonal transport causing the accumulation of material synthesized within the perikaryon. Our procedure is to expose the lumbar enlargement by partial laminectomies, open the dura, and apply a pledget soaked in colchicine (10 mg/ml, in sterile saline) to the cord dorsum for 1 hr. The pledget is then removed and the incision closed. Following a survival time of 24 hrs. the animal is sacrificed, perfused, and the spinal cord removed and sectioned. ENK is visualized using Sternberger's PAP method with diaminobenzidine as the chromagen. All antisera incubations and intervening washes include 1-3% normal goat serum to saturate non-specific binding and the detergent Triton to promote the antisera's penetration through the tissue. As controls, (1) the tissue is incubated with enkephalin antiserum that has been saturated with synthetic leucine enkephalin, or (2) the incubation with the primary antiserum is omitted.

Major Findings:

DCPST neurons

The retrograde HRP studies showed that these neurons were most numerous within a band that extended dorsoventrally for about 115 μm . This band was largely within lamina IV (with a small excursion into lamina III) throughout most of the dorsal horn. Near the dorsal horn's medial border, however, the band shifted ventrally into lamina V. Retrogradely labelled cells were also found in the grey matter adjacent to the central canal and, very rarely, within lamina I. The ventral horn neurons that are labelled by HRP injections into the dorsal column nuclei (the site of termination for most DCPST cells) were not labelled. In order to examine the possibility that our cells were labelled by HRP that had diffused outside of the partial DC transection, we performed two control experiments. In the first control experiment, we completely transected the DC caudal to the site of HRP placement. Not a single cell was retrogradely labelled in the lumbosacral enlargement of this case. In the second experiment, we made a total bilateral transection of the dorsolateral funiculi caudal to the partial DC transection. This lesion would block axonally transported HRP in any spinocervical tract neurons that may have been exposed to HRP that diffused from the partial DC transection into the adjacent dorsolateral funiculi. The number and position of retrogradely labelled cells in this experiment was unchanged,

sparse, dorsally-directed dendritic arbors. A few cells had distal dendrites within lamina IIb, but most dendrites were within lamina III. Especially well-stained cases had many dendritic spines, particularly along the distal dendrites. In those cases in which the axon was stained it was seen to issue several collaterals that coursed within lamina III. A few collaterals were traced into adjacent laminae.

In our electrophysiological investigations of lamina III neurons, we have found a population of cells that are innervated exclusively by low threshold mechanoreceptive primary afferents, with A beta axons. These cells have very small (often only a few mm²) RFs. They appear to receive exclusive input from rapidly adapting primary afferents that innervate the skin and guard hairs. They often fail to follow repeated natural stimulation and could not be driven by electrical stimulation of the RF, peripheral nerve, or dorsal columns at frequencies exceeding 20 Hz. This is noteworthy because the relevant primary afferents and other laminae III-V neurons that are innervated by such afferents are capable of following electrical stimuli at frequencies exceeding several hundred Hz. Several of the physiologically characterized lamina III neurons have been impaled and intracellularly stained with HRP. In all aspects of their morphology they are identical to the cells stained by the extracellular HRP and immunocytochemical methods. Our observations of a population of lamina III interneurons that are excited by low intensity mechanical stimulation and that are immunoreactive for enkephalin suggests a possible mechanism for the well known inhibitory effects that low threshold mechanoreceptor activation exerts on nociceptive dorsal horn neurons.

Lamina II neurons

Our immunocytochemical studies have confirmed the observations of others that lamina II contains enkephalin immunoreactive perikarya. However, the specific type (or types) of lamina II neuron that contains ENK is not known. In material from colchicine pre-treated cats we observed ENK neurons in lamina IIb whose proximal dendritic arbors clearly resembled the lamina IIb islet cells that have been defined by Golgi and intracellular HRP studies from this laboratory. In collaborative EM studies with Drs. Ruda and Gobel we have shown that the dendrites of intracellularly stained lamina IIb islet cells contain synaptic vesicles and that these dendrites are involved in lamina IIb glomeruli. Lamina IIb dendrites that have been immunocytochemically labelled for ENK have identical synaptic vesicles and also enter into lamina IIb glomeruli. Taken together, these observations suggest that ENK neurons in lamina IIb are islet cells.

Significance to Biomedical Research and the Program of the Institute:

Several neuropathies (e.g., trigeminal neuralgia) and many diseases are accompanied by symptoms of intractable pain. Therapy for most of these conditions is neither satisfactory nor curative. Our work endeavors to delineate the neural circuitry that mediates nociception in the normal

showing that the labelled cells were not inadvertently labelled spino-cervical tract neurons. In one experiment, all of the labelled cells that had clearly visible nuclei were counted in a complete serially sectioned series from segment L₇. We found an average of 41.5 neurons in each unilateral millimeter of the segment's rostrocaudal extent. This is about equal to published estimates of the density of spino-cervical tract neurons and about one-third of the estimated density of spinothalamic tract neurons. Thus, it is clear that the DCPST is a major somatosensory projection system in the cat.

Electrophysiological studies of antidromically identified DCPST neurons have shown that about one-half of these cells are innervated only by low threshold mechanoreceptive primary afferents. The other one-half were excited by low threshold mechanoreceptive primary afferents but these cells also responded with a maintained increased discharge frequency to noxious pinch. Electrical stimulation of their RFs failed to reveal any evidence that they received input from unmyelinated primary afferents. Thus, we conclude that the nociceptive innervation of these cells comes exclusively from high threshold mechanoreceptive primary afferents with myelinated axons. Several of the antidromically identified DCPST neurons were successfully impaled and intracellularly stained with HRP. Their perikarya were found throughout lamina IV. Their dendritic arbors were elongated rostrocaudally (up to 1,450 μm), but relatively compressed mediolaterally (generally about 450 μm). Although a few cells had apical dendrites that penetrated lamina II, none of the cells had any appreciable amount of dendritic surface within lamina II. The axons of two cells were very well stained and issued varicosity-bearing axon collaterals that coursed through lamina IV and into lamina V. Thus, at least some DCPST neurons issue synapses into local circuits.

Small interneurons in lamina III

The immunocytochemical studies revealed numerous small ENK neurons within lamina III. The neurons had perikarya ranging from 6 to 15 μm . In most cases large primary dendrites issued from the perikaryon's rostral and caudal poles. These large primary dendrites generally traveled in the long axis of the cord while sweeping dorsally. These neurons were not rare; with a magnification of 250X we generally saw 3-8 cells in a single field. The immunocytochemical staining was of excellent quality, nevertheless it was not possible to see the cells' dendritic arbors past the branch point of secondary (and occasionally tertiary) dendrites.

In order to more completely visualize the small lamina III neurons' morphology we made small extracellular HRP deposits in lamina III via micropipettes. We recovered several neurons stained by this method; their complete dendritic arbors and often their axon and axon collaterals were visible. Their perikarya and proximal dendritic arbors were identical with the immunocytochemically stained cells. They generated

state. We anticipate that this knowledge will be the foundation of our understanding of pain pathologies.

Proposed Course: We intend to extend this work along several parallel paths. Our work on the DCPST neurons will be extended to an electrophysiological analysis of intracellular potentials. We are also contemplating an examination of the anatomical relationship between DCPST neurons and spinocervical tract neurons. Both of these systems originate from lamina IV neurons. Are they randomly interspersed or is there some regularity in their positions within the lamina? Do some lamina IV neurons send axons into both tracts? We have also begun to immunocytochemically identify some of the synaptic input to DCPST neurons.

Our evidence concerning the physiological and morphological identity of enkephalinergic lamina IIb islet cells and lamina III interneurons is strong but essentially indirect. We will attempt to make these identifications unequivocal by intracellularly labelling physiologically characterized neurons and subsequently "double" labelling them with the immunocytochemical method. The identity of the other enkephalinergic lamina II neurons will also be investigated.

2. Publications:

Bennett, G.J., Abdelmoumene, M., Hayashi, H. and Dubner, R.: Physiology and morphology of substantia gelatinosa neurons intracellularly stained with horseradish peroxidase. J. Comp. Neurol., 1980, 194:809-827.

Bennett, G.J., Abdelmoumene, M., Hayashi, H., Hoffert, M.J. and Dubner, R.: Spinal cord layer I neurons with axon collaterals that generate local arbors. Brain Res., 1981, 209:421-426.

Abdelmoumene, M., Bennett, G.J., Hayashi, H., Gobel, S., Falls, W.M., Humphrey, E. and Dubner, R.: Substantia gelatinosa interneurons. Proc. of IUPS Satellite Symposium on Dorsal Horn, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00291-02 NA																		
PERIOD COVERED <p style="text-align: center;">October 1, 1980 to September 30, 1981</p>																				
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">Neural Correlates of Behavior in the Monkey Medullary Dorsal Horn</p>																				
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 40%;">Bushnell, M.C.</td> <td style="width: 40%;">Staff Fellow</td> <td style="width: 20%;">NIDR NA</td> </tr> <tr> <td>Duncan, G.H.</td> <td>Sr. Asst. Dental Surgeon</td> <td>NIDR NA</td> </tr> <tr> <td>Dubner, R.</td> <td>Chief, NAB</td> <td>NIDR NA</td> </tr> <tr> <td>He, L.F.</td> <td>WHO International Fellow</td> <td>NIDR NA</td> </tr> <tr> <td>Taylor, M.B.</td> <td>Animal Caretaker</td> <td>NIDR NA</td> </tr> <tr> <td>Ziriaux, J.M.</td> <td>Psychologist</td> <td>NIDR NA</td> </tr> </table>			Bushnell, M.C.	Staff Fellow	NIDR NA	Duncan, G.H.	Sr. Asst. Dental Surgeon	NIDR NA	Dubner, R.	Chief, NAB	NIDR NA	He, L.F.	WHO International Fellow	NIDR NA	Taylor, M.B.	Animal Caretaker	NIDR NA	Ziriaux, J.M.	Psychologist	NIDR NA
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TOTAL MANYEARS: <p style="text-align: center;">4.45</p>	PROFESSIONAL: <p style="text-align: center;">2.65</p>	OTHER: <p style="text-align: center;">1.80</p>																		
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>																				
SUMMARY OF WORK (200 words or less - underline keywords) <p> This project studies the effect of behavioral and environmental variables on responses of thalamic projection neurons in the <u>medullary dorsal horn</u> (<u>trigeminal nucleus caudalis</u>) to noxious and innocuous thermal stimuli. <u>Rhesus monkeys</u> are trained to detect the termination of innocuous heat stimuli and the onset of noxious heat stimuli. In a second task, these monkeys detect the onset of a light stimulus. Other monkeys are being trained to discriminate which of two simultaneously presented heat pulses is hotter and which of two simultaneously presented lights is brighter. <u>Trigeminothalamic neurons</u> code thermal discriminative information used by the monkey within the behavioral tasks. Some neurons that respond to passive mechanical and thermal stimulation also respond to other stimuli the monkey uses for successful completion of the task. We observe several patterns of task-related activity, and some neurons showing each pattern project to the thalamus. These task-related responses may modulate sensory activity and thereby influence the perception of and response to <u>oral-facial pain</u>. </p>																				

1. Project Description:

Objectives: This project was designed to study the response characteristics of trigeminothalamic neurons in alert, behaving monkeys. One objective is to ascertain in alert monkeys the sensory-discriminative properties of thermally sensitive neurons that send projections to the thalamus. Another objective is to study responses of trigeminothalamic neurons related to events within a behavioral task. Such task-related responses have been observed previously by this group in medullary dorsal horn (trigeminal nucleus caudalis) neurons, but have not been examined in known thalamic projection neurons.

Methods Employed: Two types of behavioral paradigms are employed to study sensory-discriminative and task-related properties of trigeminothalamic neurons: (1) detection tasks and (2) discrimination tasks.

Detection tasks

In these tasks, which have been described previously, monkeys are trained to detect changes in thermal and visual stimuli. In the thermal detection task, monkeys are trained to detect the termination of innocuous heat pulses applied to a 1-cm diameter contact thermode on the monkey's face. The baseline temperature of the probe is 35°C. At the beginning of each trial a panel is illuminated. The monkey presses the lighted panel and is presented an innocuous heat pulse of 37°, 39°, 41°, or 43°C. The pulse lasts for a random duration (2-8 sec), and then the probe temperature returns to 35°C. The monkey receives a water reward for releasing the panel within 2 sec of the heat pulse termination. After the monkey learns this task, noxious heat pulses (45°, 47°, and 49°C) are also presented on approximately 20% of trials. On these trials the monkey does not receive a reward for detecting the termination of the noxious temperature. Instead, he terminates the noxious heat pulse by releasing the panel, thereby escaping the stimulus.

The visual detection task requires the monkey to detect the onset of a light stimulus. At the beginning of a trial the monkey presses the illuminated panel, as in the thermal detection task. After a random time (2-8 sec) a second panel is illuminated. The monkey receives a water reward for releasing the first panel within 2 sec of the second light onset. In some experiments the thermode is removed from the monkey's face and in others it is placed on the face. When on the face, the thermode sometimes remains at 35°C, and at other times behaviorally irrelevant heat pulses are presented. The visual task is used to study responses of trigeminothalamic neurons that are related to important behavioral and stimulus events, i.e., task-related responses. We also can assess the effect of stimulus significance on thermal responses of neurons by comparing the neuronal response to a behaviorally relevant thermal stimulus in the thermal task and that to a behaviorally irrelevant thermal stimulus in the visual task.

Discrimination tasks

In these tasks monkeys are trained to discriminate small differences in intensity of thermal or visual stimuli. The thermal discrimination task requires that monkeys report which of two simultaneously-applied heat pulses is warmer. Two 1-cm diameter contact thermodes are positioned symmetrically on the monkey's face. The baseline temperature of the probe is 35°C. At the beginning of each trial a panel is illuminated. The monkey presses the illuminated panel and is presented simultaneous heat pulses, one on each probe. The rise-time slopes of the pulses are identical, but the final temperatures differ. The heat pulses range from 37° to 49°C. After a variable time (4-8 sec) the thermodes return to 35°C and two side panels are illuminated. The monkey receives a water reward for pressing within two seconds the left panel if the thermode on the left side of the face was warmer or the right panel if the right thermode was warmer. This task provides a psychophysical measure to determine difference limens for thermal intensities in the innocuous and noxious ranges. It is especially useful for the study of thermally responsive neurons to determine which neurons show differential responses to the smallest thermal intensity differences discriminable by the monkey.

The visual discrimination task requires the monkeys to report which of two simultaneously presented visual stimuli is brighter. At the beginning of a trial the monkey presses the illuminated center panel and is presented simultaneous lights of different intensities, one above each of the two unlit side response panels. After a variable time (4-8 sec) the stimulus lights terminate and the side response panels are illuminated. The monkey receives a water reward for pressing the left response panel if the left stimulus light was brighter and the right response panel if the right stimulus light was brighter. The visual task provides a useful comparison to the thermal discrimination task. Thermal responses should be absent in this task, but task-related responses such as have been observed in the medullary dorsal horn using the detection tasks might be present in the visual discrimination task. This task can be used to study neuronal responses that are associated with significant stimulus and behavioral events particularly in neurons that transmit discriminative thermal information to the thalamus.

Two monkeys are currently being trained on the thermal and visual discrimination tasks. However, no neural data have been recorded while the monkey performs these tasks.

Recording procedures. After the monkeys learn the behavioral tasks, they are prepared for extracellular single unit recording. A head holding apparatus and sealed chamber are surgically attached to the monkey's skull, stimulating electrodes are introduced stereotaxically into the ventroposterior medial thalamic nucleus, and EMG electrodes are inserted into the lip musculature. After recovery from surgery, removable microelectrodes are introduced daily through the sealed chamber into the

medullary dorsal horn, and single unit activity is recorded while the monkey performs his task. Neural activity is then correlated with stimulus and behavioral events such as panel light onset, panel press, temperature increase, stimulus light onset, temperature decrease, panel release and delivery of reward.

Major Findings: Both sensory-discriminative and task-related properties of trigeminothalamic neurons have been studied. We found that in awake monkeys, as previously found in anesthetized monkeys, two types of trigeminothalamic neurons are responsive to noxious thermal stimuli: wide dynamic range (WDR) neurons, which respond differentially to innocuous and noxious mechanical stimuli, and nociceptive specific (NS) neurons, which respond exclusively to intense or noxious stimuli. Thermal response thresholds range from 41° to 47°C, and stimulus-response functions are monotonic from threshold to 49°C. For both WDR and NS trigeminothalamic neurons, greater neuronal discharges are associated with shorter behavioral discrimination latencies. These data show that thermally sensitive WDR and NS neurons transmit information to the thalamus which correlates with the monkey's ability to discriminate noxious thermal stimuli. Therefore, these neurons appear to participate in neural mechanisms underlying the sensory-discriminative aspects of pain.

Previously, we have described responses of thermosensitive and mechanosensitive medullary dorsal horn neurons that are independent of stimulus modality or stimulus parameters. In the present project we investigated these task-related properties in more detail and identified at least one output pathway of these neurons.

Some medullary dorsal horn neurons responsive to mechanical or thermal stimuli also show responses associated with behavioral and stimulus events within the task. We identified several types of these task-related responses. Some cells discharge when the monkey initiates the trial. Others discharge at the signal for panel release, whether that signal is a temperature change or light onset. The most common pattern of task-related activity is a transient or sustained discharge at trial initiation and an additional burst discharge after the signal for panel release. Task-related responses occur only during performance of a task and are related to sensory events that lead to successful completion of the task. Such responses are not correlated with specific face, arm or hand movements. Some neurons with each pattern of task-related activity project to the thalamus.

Neurons with task-related activity may be providing a gain control mechanism for somatosensory information that the animal must use for successful completion of the task. Additionally, these responses may be involved in the transmission of behavioral information to motor cortex to facilitate appropriate goal-directed behavior.

Significance to Biomedical Research and the Program of the Institute: These studies are important in determining the neural substrate of orofacial pain. By studying monkeys' behavioral responses within a task we

can assess the influence upon pain perception of such variables as significance and predictability of noxious thermal stimuli, as well as determine which neurons provide behaviorally useful sensory-discriminative information. Concurrently, we can study modulation in activity of neurons involved in the transmission of nociception information from the face. Our data show that the neural representation of oral-facial nociception can be influenced by environmental and behavioral factors at the earliest stage of central integration and that this modulatory information is relayed to a thalamic nucleus that receives thermal sensory information. This work demonstrates non-pharmacological modulation of neurons involved in oral-facial nociception, and consequently is important in understanding non-pharmacological approaches to the control of oral-facial pain.

Proposed Course: Future experiments include the following: (1) comparing the discriminative capabilities of thermally responsive WDR and NS neurons in lamina I versus deeper laminae while the monkey performs the thermal discrimination task in order to understand better the roles of these various neurons in pain discrimination; (2) the study of possible mechanisms by which behavioral factors influence nociceptive neurons. This investigation includes assessing the effects of (a) pharmacological manipulations, such as systemic administration of various neuropeptides, and (b) electrical stimulation of reticular and cortical inputs to the medullary dorsal horn during behavioral responses in the thermal and visual tasks; (3) the study of nociceptive neurons in the ventroposterior medial thalamus, somatosensory cortex and lateral posterior parietal cortex in behaving monkeys.

2. Publications:

Hoffman, D.S., Dubner, R., Hayes, R.L. and Medlin, T.P.: Neuronal activity in the medullary dorsal horn of awake monkeys trained in a thermal discrimination task. I. Responses to innocuous and noxious thermal stimuli. J. Neurophysiol., 46:409-427, 1981.

Hayes, R.L., Dubner, R. and Hoffman, D.S.: Neuronal activity in the medullary dorsal horn in awake monkeys trained in a thermal discrimination task. II. Behavioral modulation of responses to thermal and mechanical stimuli. J. Neurophysiol., 46:428-433, 1981.

Dubner, R., Hoffman, D.S. and Hayes, R.L.: Neuronal activity in the medullary dorsal horn of awake monkeys trained in a thermal discrimination task. III. Task-related responses and their functional role. J. Neurophysiol., 46:444-464, 1981.

Dubner, R.: Peripheral and central mechanisms of pain. Pain, Discomfort and Humanitarian Care, edited by L. Ng and J. Bonica, Elsevier/North Holland Biomedical Press, 1980, pp. 61-82.

Dubner, R., Hoffman, D.S. and Hayes, R.L.: Neural correlates of behavior in the monkey caudal medulla. Oral-Facial Sensory and Motor Functions, edited by Y. Kawamura and R. Dubner, Quintessence, Tokyo, 1981, in press.

Sumino, R. and Dubner, R.: Response characteristics of specific thermoreceptive afferents innervating monkey facial skin and their relationship to human thermal sensitivity. Br. Res. Rev., in press.

Sessle, B.J., Hu, J.W., Dubner, R. and Lucier, G.E.: Functional properties of neurons in cat trigeminal subnucleus caudalis (medullary dorsal horn). II. Modulation of responses to noxious and nonnoxious stimuli by periaqueductal gray, nucleus raphe magnus, cerebral cortex and afferent influences, and effect of naloxone. J. Neurophysiol., 45:193-207, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00312-01 NA												
PERIOD COVERED <p style="text-align: center;">March 15, 1981 to September 30, 1981</p>														
TITLE OF PROJECT (80 characters or less) <p style="text-align: center;">Physiology, Morphology and Immunocytochemistry of Spinal Dorsal Horn Lamina I Neurons</p>														
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT														
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Hoffert, M.J.</td> <td style="width: 33%;">Senior Staff Fellow</td> <td style="width: 33%;">NIDR NA</td> </tr> <tr> <td>Miletic, V.</td> <td>Postdoctoral Fellow</td> <td>NIDR NA</td> </tr> <tr> <td>Dubner, R.</td> <td>Chief, NAB</td> <td>NIDR NA</td> </tr> <tr> <td>Ruda, M.A.</td> <td>Senior Staff Fellow</td> <td>NIDR NA</td> </tr> </table>			Hoffert, M.J.	Senior Staff Fellow	NIDR NA	Miletic, V.	Postdoctoral Fellow	NIDR NA	Dubner, R.	Chief, NAB	NIDR NA	Ruda, M.A.	Senior Staff Fellow	NIDR NA
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Miletic, V.	Postdoctoral Fellow	NIDR NA												
Dubner, R.	Chief, NAB	NIDR NA												
Ruda, M.A.	Senior Staff Fellow	NIDR NA												
COOPERATING UNITS (if any)														
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<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS														
SUMMARY OF WORK (200 words or less - underline keywords)														
<p> <u>Neurons in lamina I and II of the lumbar spinal cord of the cat were character-</u> <u>ized physiologically in terms of responsiveness to various natural stimuli</u> <u>(such as pinch and brush), peripheral input (C fiber vs. Aδ vs. Aβ), and</u> <u>projection sites. These neurons were then intracellularly injected with</u> <u>horseradish peroxidase, the cats perfused, and the spinal cord sectioned and</u> <u>reacted with diaminobenzadine. The neurons were identified, the tissue</u> <u>processed immunohistochemically with antibodies to serotonin, substance P,</u> <u>enkephalin, and somatostatin, and the cells and immunoreactive boutons then</u> <u>drawn by camera lucida technique with high power light microscopy.</u> </p>														

1. Project Description:

Objectives: Many lines of evidence implicate neurons of spinal cord lamina I in nociception. Lamina I is innervated by small primary afferent fibers, both myelinated and unmyelinated, and including substance P containing fibers. Lamina I receives descending serotonergic and noradrenergic projections from the brainstem, both of which have been implicated in various analgesic mechanisms. Most importantly, lamina I neurons characterized physiologically respond either to noxious stimuli (NS) only, or to both noxious and innocuous stimuli differentially (WDR).

Other isolated data exist about lamina I. The neurons of lamina I are varied in size and morphology. They project axons to various targets, especially thalamus and cerebellum. Other possible neurotransmitters have been associated with lamina I, including somatostatin and enkephalin.

The heterogenicity of inputs, cell types, neurotransmitters, and projection sites suggests that there may well be identifiable subgroups of lamina I neurons with specific clusters of those various characteristics.

This project is designed to investigate that issue, by examining responsiveness to natural stimuli, electrical parameters of peripheral input, projection sites, immunohistochemical staining, and cellular morphology, all in the same neuron, for a population of lamina I neurons.

In the process of obtaining the above data, neurons in lamina II are occasionally recovered. Issues analogous to those described above exist for lamina II, and lamina II also is an area of particular interest. Therefore, lamina II neurons recovered in the course of this study are processed similarly.

Methods Employed: Adult cats are anesthetized, first with ketamine, then with pentobarbital, artificially ventilated, and catheterized arterially and venously. Blood pressure and expired CO₂ are monitored.

A limited lumbar laminectomy is employed to expose the lumbosacral enlargement of the spinal cord. Craniotomy is used to access the thalamus, high cervical laminectomy with low craniotomy to access the cerebellum, and/or thoracic laminectomy to access the thoracic spinal cord.

A comb of four thalamic electrodes is placed in the medial and lateral thalamus by stereotaxic technique and by monitoring evoked potentials. Bipolar cerebellar electrodes are placed in the lateral posterior vermis by direct visualization and by monitoring evoked potentials. Bipolar thoracic cord electrodes bridge the cord and are placed by direct visualization.

Glass micropipettes filled with 0.2 M KCl and 6% HRP are used in the lumbar spinal cord. The electrodes are slowly introduced into the superficial dorsal cord concurrent with pulsed electrical stimulation of the sciatic nerve. When a neuron's electrical activity is clearly isolated, it's responsiveness to natural stimuli and electrical characteristics of peripheral input are characterized extracellularly, and stimulation is attempted from thalamus, cerebellum and/or thoracic cord. The neuron is then penetrated, quickly reevaluated to confirm its identity, and then injected iontophoretically with HRP.

Only one injection attempt is made per cord patch, to insure unequivocal identification. Within four hours of the first injection attempt, the patches are marked with green dye, the cat is perfused with fixative, and the spinal cord is removed and stored in buffer.

The next day, the spinal cord is trimmed, sectioned parasagittally in 50 μ m sections, reacted with diaminobenzadine (DAB) intensified with cobalt chloride, and washed through a graded series of glycerin. Recovered neurons are identified and classified. Sections containing lamina I neurons are exposed to antibodies directed against serotonin or substance P. When a neuron appears on several sections, both antibodies can be used. In the future, some of these sections will be exposed to antibodies to enkephalin. Deeper neurons are exposed to antibodies to somatostatin or enkephalin.

These sections are then exposed to peroxidase-linked antibodies directed against the primary antibodies described above. The tissue is then reacted again with DAB, but without cobalt chloride. This procedure produces dark blue-stained neurons, and golden brown stained neurochemically identified axons and presynaptic boutons. Cells and appropriate immunoreactive boutons are drawn in detail by camera lucida technique with high power light microscopy.

Major Findings: All of the following findings are preliminary, and need to be confirmed by further study.

No neurons have been found that receive overwhelming innervation by any one neurotransmitter studied. However, certain patterns are emerging. Descending inhibitory axons, represented by serotonin, appear to have a characteristic pattern of dendritic contact easily distinguishable from the contact pattern displayed by primary afferent innervation, represented by substance P and somatostatin.

There is a clear heterogenicity of innervation by the different axon types within the neural population being studied. It is too early to state what the best predictors of neurotransmitter innervation are. We will continue to utilize multiple stimulation procedures to evaluate the functional characteristics of various cell types and attempt to relate this to chemical mediation.

Significance to Biomedical Research and the Program of the Institute:

Pain is a major component of many disease states, as well as an inevitable side effect of most surgical and dental procedures. Advances in pain management will be facilitated by a better understanding of the basic processes of nociception. This study provides new and significant information about the pharmacology, physiology, and anatomy of a major neural circuit involved in nociception--the integration and processing of information at the level of the superficial dorsal horn of the spinal cord.

Proposed Course: We continue to gather information about lamina I neurons as described above. No significant changes are planned at this preliminary stage of the project.

2. Publications:

None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00132-07 NA															
PERIOD COVERED <div style="display: flex; justify-content: space-between;"> October 1, 1980 to September 30, 1981 CT 0060102 </div>																	
TITLE OF PROJECT (80 characters or less) Evaluation of Anti-Anxiety Agents as Alternatives to General Anesthesia for Ambulatory Patients																	
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 40%;">Dionne, R.A.</td> <td style="width: 40%;">Staff Fellow</td> <td style="width: 20%;">NIDR NA</td> </tr> <tr> <td>Sisk, A.</td> <td>Sr. Asst. Dental Surgeon</td> <td>NIDR NA</td> </tr> <tr> <td>Wirdzek, P.R.</td> <td>Clinical Nurse</td> <td>NIDR NA</td> </tr> <tr> <td>Gracely, R.H.</td> <td>Research Psychologist</td> <td>NIDR NA</td> </tr> <tr> <td>Clark, B.A.</td> <td>Clinical Nurse</td> <td>NIDR NA</td> </tr> </table>			Dionne, R.A.	Staff Fellow	NIDR NA	Sisk, A.	Sr. Asst. Dental Surgeon	NIDR NA	Wirdzek, P.R.	Clinical Nurse	NIDR NA	Gracely, R.H.	Research Psychologist	NIDR NA	Clark, B.A.	Clinical Nurse	NIDR NA
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COOPERATING UNITS (if any)																	
LAB/BRANCH Neurobiology and Anesthesiology Branch																	
SECTION Clinical Pain Section																	
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205																	
TOTAL MANYEARS: 1.70	PROFESSIONAL: 1.10	OTHER: .60															
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div>																	
SUMMARY OF WORK (200 words or less - underline keywords) The purpose of this project is 1) to objectively evaluate the <u>efficacy</u> and <u>clinical toxicity</u> of drugs given to outpatients to alleviate apprehension associated with dental procedures, 2) to study the physiological and biochemical responses to the stress of dental therapy, and 3) to evaluate the role of <u>exogenous epinephrine</u> administered with <u>local anesthetic</u> on <u>cardiovascular</u> performance. Special attention has been given to the non-invasive measurement of cardiac output and stroke volume by thoracic impedance cardiography. A recent study employing this methodology indicates that exogenous epinephrine administered with local anesthesia results in a <u>five-fold increase in circulating epinephrine levels</u> and that there is a concomitant increase in cardiac output. A parallel investigation indicated that the elevated epinephrine levels and elevated cardiac output is not attenuated by diazepam premedication. <u>Diazepam premedication</u> does appear to <u>suppress</u> the elevation in circulating <u>norepinephrine levels</u> seen in non-sedated patients. These findings suggest that exogenously administered epinephrine results in an increase in circulating levels and a resultant increase in cardiac output.																	

1. Project Description:

Objectives: The prime objective of this project is to evaluate the efficacy and clinical manifestations of toxicity of drugs given to dental outpatients as alternatives to general anesthesia. Measures of efficacy assessed include relief of anxiety, analgesia, amnesia and patient cooperation. Measures of clinical toxicity assessed include arterial oxygen saturation, respiratory rate, blood pressure, cardiac output, stroke volume, heart rate, impairment of psychomotor and cognitive function and non-specific central nervous system depression. By comparing the relationship between efficacy and toxicity, it is possible to identify agents or combinations of agents which have genuine therapeutic advantage. Such information allows the rational selection of drugs for use in different clinical situations, for patients of varying anxiety levels and for safety in the hands of clinicians of different training levels. In addition, this therapeutic ratio provides an objective method for assessing new agents proposed for the relief of acute pain and apprehension.

Secondary objectives of this project include utilizing these assessment techniques to study the physiological and biochemical responses to the stress of surgery, the effect of exogenous epinephrine administered with local anesthesia and the effect of anti-anxiety drugs on these two phenomena. Technological advances such as the impedance cardiograph and sensitive assays for epinephrine and norepinephrine permit a re-examination of the effect of surgical stress, exogenous epinephrine and their interaction with intravenous anti-anxiety drugs not previously possible in outpatients undergoing a dental procedure.

Methods Employed: Patients undergoing the removal of impacted third molars serve as experimental subjects for these investigations. Patients are screened to confirm the need for extraction, a complete medical history and physical examination performed and the surgical procedure is conducted in the NIDR Dental Clinic in accordance with normal clinical care.

Physiological response is monitored non-invasively to avoid introducing anxiety and morbidity which can be associated with invasive techniques. Oxygen saturation is recorded via an earpiece oximeter, blood pressure via an automatic blood pressure recorder, and heart rate, stroke volume and cardiac output with an impedance cardiograph. Continuous readings are taken during a baseline period, through surgery, and post-operatively.

Plasma samples for the measurement of epinephrine and norepinephrine are collected under non-stressful conditions several days prior to surgery, immediately prior to surgery, following local anesthetic injection, during surgery, and approximately 3 hours after surgery.

Samples are stored in ice, centrifuged and frozen until assayed by high-pressure liquid chromatography with electro-chemical detection. A battery of traditional and novel scales are used to assess intra- and post-operative pain and anxiety levels.

Major Findings: Previous work has indicated that the combination of diazepam, fentanyl and methohexital results in respiratory depression and a transient decrease in stroke volume without demonstrating a clear advantage over other combinations in terms of efficacy. More recent work has demonstrated that epinephrine administered with local anesthetic results in a five-fold increase in circulating epinephrine levels when compared to local anesthetic without epinephrine. Concomittant with this increase in circulating epinephrine levels is an increase in cardiac output, as measured by impedance cardiography, which is not seen in the group receiving local anesthetic without epinephrine. The stress of surgery was associated with increase in heart rate, systolic blood pressure and cardiac output.

Premedication with diazepam did not attenuate the increased circulating epinephrine levels following local anesthesia or the increase cardiac output. Diazepam does prevent the stress-induced elevation in circulating norepinephrine levels seen in non-sedated patients, presumably by preventing sympathetic arousal.

These findings suggest that exogenously administered epinephrine with local anesthetic is being absorbed in sufficient amounts to result in measureable circulatory changes. These changes are not being attenuated by relatively large doses of intravenous diazepam, further suggesting that the increased epinephrine levels are independent of the stress of surgery. Diazepam does, however, block the sympathetic induced increase in circulating norepinephrine levels. These findings suggest that the traditional view of the effects of epinephrine in local anesthetics is in need of re-evaluation.

Significance to Biomedical Research and the Program of the Institute: Research to date under this protocol has resulted in the development of techniques which are useful for assessing the therapeutic and toxic effects of drugs given to dental outpatients. This research has also resulted in a body of knowledge on the effects of the various sedative and anesthetic drugs tested.

The delivery of dental care and the maintenance of oral health is contingent upon regular professional care. It is generally accepted that apprehension about the pain associated with dental care causes a portion of the population to avoid or postpone dental care. Intravenous sedation is a technique for overcoming patient apprehension and minimizing any perception or memory of pain. Through these investigations, we have been able to identify these drugs and combinations which are effective for achieving these goals with a minimum potential for clinical toxicity.

We have also elicited new information on the circulatory effects of epinephrine in local anesthetics. While these changes are well-tolerated in healthy, young volunteers, they may not be so innocuous in the elderly or cardiovascular risk patient. Because tens of thousands of local anesthetics are administered daily and the rationale for including epinephrine in local anesthetics for restorative procedures is not obvious, it is worthwhile to examine this potential risk factor.

Proposed Course: Future studies are aimed at assessing the efficacy and potential toxicity of existing and novel anti-anxiety agents. The overall goal of these investigations will be to develop methods for controlling pain and apprehension which have minimal risk for the patient and require minimal additional training for the clinician. Parallel investigations will further evaluate the circulation effects of epinephrine administered with local anesthetics to dental outpatients.

2. Publications:

Gelfman, S.S., Gracely, R.H., Driscoll, E.J., Butler, D.P., Sweet, J.B. and Wirdzek, P.R.: Recovery following intravenous sedation during dental surgery performed under local anesthesia. Anesth. Analg., 59: 775-781, 1980.

Dionne, R.A., Driscoll, E.J., Gelfman, S.S., Sweet, J.B., Butler, D.P. and Wirdzek, P.R.: Cardiovascular and respiratory response to intravenous diazepam, fentanyl and methohexital in dental outpatients. J. Oral Surg., 39:343-349, 1981.

Goldstein, D.S., Dionne, R.A., Sweet, J., Gracely, R.H., Brewer, H.P., Gregg, R. and Keiser, H.R.: Circulatory, plasma catecholamine, cortisol, lipid, and psychological responses to a real-life stress (third molar extractions): Effect of diazepam sedation and of inclusion of epinephrine with the local anesthetic. Psychosomatic Med., in press.

Dionne, R.A.: Diazepam-induced thrombophlebitis (Letter). J.A.D.A., 102:824, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 DE 00133-07 NA																		
PERIOD COVERED October 1, 1980 to September 30, 1981		CT 0060101																		
TITLE OF PROJECT (80 characters or less) Assessment of experimental and clinical pain																				
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Gracely, R.H.</td> <td style="width: 33%;">Research Psychologist</td> <td style="width: 33%;">NIDR NA</td> </tr> <tr> <td>Dionne, R.A.</td> <td>Staff Fellow</td> <td>NIDR NA</td> </tr> <tr> <td>Dubner, R.</td> <td>Chief, NAB</td> <td>NIDR NA</td> </tr> <tr> <td>Heft, M.W.</td> <td>Postdoctoral Fellow</td> <td>NIDR NA</td> </tr> <tr> <td>Wolskee, P.J.</td> <td>Psychologist</td> <td>NIDR NA</td> </tr> <tr> <td>Sisk, A.</td> <td>Sr. Asst. Dental Surgeon</td> <td>NIDR NA</td> </tr> </table>			Gracely, R.H.	Research Psychologist	NIDR NA	Dionne, R.A.	Staff Fellow	NIDR NA	Dubner, R.	Chief, NAB	NIDR NA	Heft, M.W.	Postdoctoral Fellow	NIDR NA	Wolskee, P.J.	Psychologist	NIDR NA	Sisk, A.	Sr. Asst. Dental Surgeon	NIDR NA
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LAB/BRANCH Neurobiology and Anesthesiology Branch																				
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INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205																				
TOTAL MANYEARS: 2.60	PROFESSIONAL: 1.10	OTHER: 1.50																		
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SUMMARY OF WORK (200 words or less - underline keywords) <p> The objectives of this project are (1) to assess <u>psychophysical methods</u> of <u>experimental pain</u> measurement, i.e., <u>magnitude estimation</u>, <u>category scaling</u>, and <u>cross-modality matching</u>. Pain will be experimentally induced by <u>electrocutaneous</u>, <u>electric tooth pulp</u>, and <u>mechanical heat</u> stimulation; (2) to assess <u>clinical pain</u> measures, such as pain questionnaires and sensory matching methods, in a dental setting; (3) to determine the validity of experimental pain models by comparison of experimental and clinical pain responses; and (4) to evaluate known <u>pharmacological</u> and <u>non-pharmacological pain-control agents</u>. </p>																				

1. Project Description

Objectives: The purpose of these studies are 1) to develop psychophysical and behavioral models of pain perception that assess the intensity and unpleasantness of experimental and clinical pain sensation and also assess the ability of subjects to judge their perceptual experience, 2) to use these models to assess the physiological and psychological mechanisms of pain and analgesia, and the efficacy of pharmacological and nonpharmacological methods of pain control.

Methods Employed: Experimental pain sensations are produced by application of electrical stimuli to intact teeth with techniques that stimulate tooth pulp afferents exclusively. Experimental sensations of heat are produced by a contact stimulator that produces thermal wave-forms with maximal cooling and warming rates of 10°C/sec. Sensations produced by experimental pain stimuli are evaluated by category scales, cross-modality matching, verbal descriptor scales, information-integration techniques, and by behavioral reaction-time methods.

In addition to experimental pain stimuli, acute postsurgical pain following third molar extractions and pain from chronic syndromes also are assessed. Both acute and chronic clinical pains are assessed by category scales, visual analog scales, verbal descriptor scales, standard pain questionnaires, and by direct sensory-matches to experimentally-produced pain sensations.

Major Findings: The study of mechanisms of postoperative dental pain is in progress. Eighty-eight patients have received third molar extractions, an additional 24 patients will complete the study. Pain is assessed for 1 hour before and after intravenous injection of fentanyl, saline, naloxone and no treatment by visual analog, verbal descriptor and descriptor differential scales of sensory intensity unpleasantness and painfulness, and by the McGill Pain Questionnaire. Preliminary results show that the effect of saline placebo in reducing the magnitude of postoperative pain was significantly greater when the placebo was alternated double blind with the administration of the narcotic fentanyl and no treatment than when it was alternated with only no treatment. This study also showed that 10 mg naloxone did not produce hyperalgesia in comparison to placebo or no treatment.

A new study used an information-integration procedure called Functional Measurement to separately assess effects of intravenous medications on the perceptual, cognitive and response mechanisms involved in using a category scale to rate the average of pain intensities evoked by electrical tooth pulp stimuli and symbolized by a word. Results show that the narcotic fentanyl reduced the perceptual intensity of tooth pulp stimuli without altering the ability to integrate or respond to the stimuli. The minor tranquilizer diazepam reduced the

cognitive ability to integrate the stimuli without altering either the perception of the stimuli or the response to these perceptions.

An additional study developed a new clinical pain scaling method, the descriptor differential scale (DDS) that applies techniques of experimental pain scaling to the assessment of clinical pain. This questionnaire provides 36 subscales anchored by verbal descriptors of sensory intensity, unpleasantness and painfulness, and requires subjects to rate their pain sensations on a 21-point scale in relation to each descriptor. This method anchors judgments to subjective standards and produces more data per observation than other methods, reducing the variability of the resultant measures. In addition, an analysis of the pattern of responses to the subscales yields a measure of scaling performance for individual subjects. Preliminary results show that the DDS is more sensitive than a visual analog scale in the assessment of placebo response to postoperative dental pain, and that it provides a sensitive measure of scaling ability.

A final study used computer simulation to model human psychophysical behavior. Simulations show that discriminability measures of pain sensations are equally sensitive to cognitive and sensory effects and thus do not, as many investigators claim, provide measures of pain or analgesia. Additional simulations have been used to identify the common factors contained in several scaling methods. Five identified factors include the gain and variability of the sensory afferent system, the magnitude and variability of the subjective criteria used to make responses, and the aversive, unpleasant emotional reactions to the sensations.

Significance to Biomedical Research and the Program of the Institute: Previous studies suggest that naloxone reverses placebo-produced analgesia of postoperative dental pain. The study assessing the effects of naloxone and placebo on postoperative dental pain, when completed, will determine if this effect is dependent on placebo administration or if naloxone also increases postoperative pain when placebo is not administered. This result will provide evidence pertaining to an alternative hypothesis that naloxone increases pain by antagonizing the effects of endogenous opiate-like compounds (endorphins) released as a consequence of the stress or trauma of surgery and that placebo reduces pain by independent mechanisms. Preliminary results do not support previous findings that naloxone produces hyperalgesia in comparison to placebo, suggesting that endorphin mechanisms do not play a significant role in placebo analgesia of dental postoperative pain. The finding that the placebo effect was altered significantly by experimental context emphasizes the role of psychological factors in placebo mechanism(s).

The separate assessment of analgesic effects on pain perception and on the response labels attached to the perception is a major but elusive goal in the development of psychophysical pain measures. The information-integration model provides a method to distinguish between the

effects of putative analgesic manipulations on pain perception, the verbal report of that perception, or the general ability to perform a pain rating and integrating task. This three stage model showed that a narcotic analgesic altered only the perceptual stage and a tranquilizer affected only the ability to perform the task. These results suggest that this model may be useful in separating the physiological effect of a pain treatment from the psychological effects resulting from the experimental situation, expectations of the subjects, and the side effects of the treatment.

The results with the DDS scale suggests that the presentation of multiple verbal subscales apply the efficiency of experimental pain scaling to the assessment of relevant, clinical pain. The DDS anchors clinical pain judgments, reduces variability by collecting more data per observation, and provides a measure of clinical scaling performance to assess the ability and motivation of the patients.

Results of the simulation model of human psychophysical behavior specified 5 variables in pain perception and assessed the sensitivity of several psychophysical methods to these variables. Results of these simulations suggest that no single psychophysical measure directly assesses analgesia, but that evidence for analgesia can be provided from the concomittant use of several methods.

Proposed Course: Experiments with the information-integration model will continue with an improved paradigm that requires less assumptions than the previous method. Both models will be used to evaluate other pharmacologic and non-pharmacologic pain control methods, such as hypnosis and nitrous oxide.

New studies will assess the sensitivity of the DDS scale to both weak and more robust pharmacological manipulations, and correlate DDS measures of psychophysical ability with experimental pain measures of ability derived for the same subjects. An analysis of the various subscales will show if sensitivity can be improved by combining the results of only selected scales. A new version will use descriptive phrases of everyday pain experiences such as headache or toothache.

The simulation studies will continue by comparing the relative effects of sensory and cognitive variability on response measures, and the influence of stimulus and response range. The goals of these studies is the development of a simulated model that closely mimics the psychophysical behavior of human subjects and that shows predictive power in novel assessment situations.

New studies will use the previously established scaling methods to assess the effectiveness of hypnotic suggestion for the relief of pain produced experimentally by electrical stimulation of the tooth pulp.

2. Publications:

Gracely, R.H.: Pain Measurement in Man. In: Pain, Discomfort and Humanitarian Care, edited by L. Ng and J.J. Bonica, Elsevier, North Holland, 1980, pp. 111-137.

Heft, M.W., Gracely, R.H., Dubner, R. and McGrath, P.A.: A Validation Model for Verbal Descriptor Scaling of Human Clinical Pain. *Pain*, 9 (1981) 363-373.

Gracely, R.H. and Dubner, R.: Pain Assessment in Humans - A Reply to Hall. *Pain*, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00245-04 NA
PERIOD COVERED <div style="display: flex; justify-content: space-between;"> October 1, 1980 to September 30, 1981 CT 0060117 </div>		
TITLE OF PROJECT (80 characters or less) Sensations Produced by Tooth Pulp Stimulation		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> Dubner, R. Gracely, R.H. </div> <div style="width: 30%;"> Chief, NAB Research Psychologist </div> <div style="width: 30%;"> NIDR NA NIDR NA </div> </div>		
COOPERATING UNITS (if any)		
LAB/BRANCH Neurobiology and Anesthesiology Branch		
SECTION Clinical Pain Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: .35	PROFESSIONAL: .15	OTHER: .20
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div> <div> <input type="checkbox"/> (b) HUMAN TISSUES </div> <div> <input type="checkbox"/> (c) NEITHER </div> </div>		
SUMMARY OF WORK (200 words or less - underline keywords) <p> The objective of this project is to determine the nature of sensations produced by <u>tooth pulp stimulation</u>. Non-pain, as well as <u>pain sensations</u> are evoked when low intensity electric current is applied to human teeth. In order to assess the role of <u>non-pain sensations</u> in the pulp--a traditionally exclusive pain system, these sensations were studied both psychologically and physiologically: 1) the minimum levels of current necessary to produce non-pain and pain sensations were determined for different frequencies of stimulating current; 2) the intensities of sensations from detection threshold to pain threshold were scaled by <u>magnitude production</u> and by <u>verbal descriptors</u>; 3) <u>electromyographic (EMG) activity</u> of the <u>masseter inhibitory period</u> was recorded during tooth pulp stimulation at both non-pain and pain currents; 4) the effect of a <u>narcotic</u> on sensations produced by tooth pulp stimulation and on the masseter inhibitory period was evaluated; and 5) the effects of a <u>conditioning electrical stimulus</u>, applied to the tooth, on sensation and on masseteric inhibitory period were determined. </p>		

1. Project Description:

Objectives: The purpose of these studies is to investigate sensations evoked by electrical tooth pulp stimulation. The tooth has been assumed to be an exclusive pain or nociceptive system, and thereby a unique model for the study of pain, pain pathways, and pain control agents. However, a wide variety of non-pain sensations (such as warmth, tingling, and pressure) is experienced when low intensity electric current is applied to human teeth. The existence of non-pain sensations, in addition to pain sensations, may indicate the presence of a sensory system distinct from a pain system, or these non-pain sensations may simply be a paresthesia and result from near threshold stimulation of an exclusive pain system. If there are two distinct sensory systems, there may be consistent differences between the levels of current sufficient to produce sensation and pain-assuming different thresholds for non-pain and pain nerve fibers. Or, the two sensory systems may differ in another neural property, temporal summation. Temporal summation can be studied by varying the frequency of stimulation (that is, the number of pulses within a stimulus train) and noting whether there is a uniform or differential effect on non-pain and pain sensations. If all sensations produced by tooth pulp stimulation have similar threshold and summation properties, it is probable that all sensations result from stimulation of one sensory system.

Another means of studying possible differences in the sensory innervation of the tooth pulp is monitoring the masseter inhibitory period, inhibition of masseter activity during sustained contraction that occurs after the tooth pulp is stimulated. This inhibition may provide physiological correlates for the non-pain and pain sensations produced by tooth pulp stimulation. Inhibitory periods produced by currents that produce definite non-pain sensations may differ from those caused by currents that produce pain sensation. In order to assess the value of these inhibitory periods as physiological correlates of sensation: 1) the reliability and stability of EM recordings of masseter activity during tooth pulp stimulation at non-pain and pain currents are determined; 2) the correlation between sensation experienced (non-pain or pain) and the inhibitory period is determined; 3) the effects of narcotic (fentanyl) on sensations experienced and on the inhibitory period are evaluated; and 4) the effects of a peripheral electrical conditioning stimulus on sensation and masseteric inhibitory period are determined.

Methods Employed: Non-pain and pain sensations were produced by electrical stimulation (1 sec trains of monopolar, monophasic, cathodal, 1 msec duration constant current pulses) delivered to the labial and the incisal edge of upper central incisors. Frequency of stimulation ranged from 5 to 500 HZ.

Detection and pain thresholds were determined, and the intensities of sensations between these thresholds were scaled by magnitude production and by verbal descriptors.

For EMG monitoring, upper central incisors were stimulated by electrical pulses of 1 msec duration, at currents ranging from detection threshold to supra-pain threshold. Subjects maintained low or high muscle activity by audio-feedback from surface electrodes placed over the masseter muscles. Activity was monitored at the onset of each pulse in a 30 pulse series; recordings were rectified and averaged.

Major Findings: The results of this study have been reported previously and are now published. Major findings are summarized below:

The threshold for the masseter inhibitory period coincided approximately with an individual's detection threshold for the tooth pulp stimulation. Three configurations of masseter inhibitory periods (Single, Double, and Merged) were produced by different stimulus intensities. However, no particular configuration was associated unequivocally with pain sensation. Increases in stimulus intensity evoked changes both in the configuration of the masseter inhibitory period and in the quality of the sensation produced. Chi square analyses showed significant, but progressively weaker, associations between: (1) masseter inhibitory period configuration and stimulus intensity; (2) quality of sensation and stimulus intensity; and (3) quality of sensation and masseter inhibitory period configuration. The weakness of the association between the quality of sensation and masseter inhibitory period also was demonstrated in a double-blind study of the effects of a narcotic analgesic, fentanyl. Although the strengths of non-pain and pain sensations were reduced significantly after fentanyl, there were no changes in the masseter inhibitory periods.

We conclude that contrary to previous reports, the masseter inhibitory period cannot be considered a reliable correlate of pain. These findings also suggest that the reflex masseter inhibition acts via pathways in the trigeminal brain stem sensory complex that are independent of opiate suppression of pain.

Significance to Biomedical Research and the Program of the Institute: Electromyographic monitoring of masseter inhibitory activity (following chin tap) has been used as a diagnostic tool for assessing temporomandibular joint dysfunction (TMJ). This inhibitory period (following tooth pulp stimulation) has been used also as a nociceptive reflex, a physiological correlate for pain. However, the present results show that the inhibitory period often is not correlated with pain sensation. The inhibitory period may be used as an index of the current applied to an un-anesthetized tooth, but not as a reliable index of pain.

Proposed Course: This study will be terminated this year.

2. Publications:

McGrath, P.A., Sharav, Y., Dubner, R. and Gracely, R.H.: Masseter inhibitory periods and sensations evoked by electrical tooth pulp stimulation. Pain, 10:1-17, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00246-04 NA						
PERIOD COVERED <p style="text-align: center;">October 1, 1980 to September 30, 1981</p>								
TITLE OF PROJECT (80 characters or less) MPD Patients and Their Behavioral Responses								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Heft, M.</td> <td style="width: 33%;">Postdoctoral Fellow</td> <td style="width: 33%;">NIDR NA</td> </tr> <tr> <td>Dubner, R.</td> <td>Chief, NAB</td> <td>NIDR NA</td> </tr> </table>			Heft, M.	Postdoctoral Fellow	NIDR NA	Dubner, R.	Chief, NAB	NIDR NA
Heft, M.	Postdoctoral Fellow	NIDR NA						
Dubner, R.	Chief, NAB	NIDR NA						
COOPERATING UNITS (if any)								
LAB/BRANCH <p style="text-align: center;">Neurobiology and Anesthesiology Branch</p>								
SECTION <p style="text-align: center;">Clinical Pain Section</p>								
INSTITUTE AND LOCATION <p style="text-align: center;">NIDR, NIH, Bethesda, Maryland 20205</p>								
TOTAL MANYEARS: <p style="text-align: center;">.70</p>	PROFESSIONAL: <p style="text-align: center;">.55</p>	OTHER: <p style="text-align: center;">.15</p>						
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<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) <p>The objectives of the present phase of this project are to compare: (1) aspects of <u>illness behavior in myofascial pain dysfunction (MPD)</u> patients and other <u>chronic pain patients</u>, and (2) the incidence of various <u>signs and symptoms</u> associated with MPD in MPD patients and in normals. Comparison between MPD patients to other chronic pain patients and normals will give insight into <u>psychosocial factors</u> which influence reports of MPD.</p>								

1. Project Description

Objectives: Numerous studies have classified the Myofascial Pain Dysfunction Syndrome (MPD) as a functional disorder of the masticatory apparatus with associated clinical signs and symptoms. Our earlier studies (see publications) comparing the latencies and durations of the masseteric inhibitory periods between patients suffering from MPD and normal subjects have given some insight into neural mechanisms associated with this malady. Sophisticated radiographic techniques such as arthroscopy have been employed to study anatomic changes in the temporomandibular joint and related structures. Associations of MPD with psychological conditions such as anxiety have been measured with various questionnaires which assess personality variables. However, few studies have considered the social psychological aspects of MPD.

The purpose of the present study is to: 1) assess the attitudes of MPD patients and other non-MPD patients towards illness, and 2) develop epidemiological measures of the incidence of signs and symptoms of MPD in samples of patients suffering from MPD and others not suffering from MPD.

Methods Employed: MPD and control patients completed Pilowsky's 62 item Illness Behavior Questionnaire (IBQ) which is scored as seven scales: 1) hypochondriasis, 2) disease conviction, 3) psychological vs. somatic perception of illness, 4) affective inhibition, 5) dysphoria, 6) denial, and 7) irritability. In addition, a head and neck examination on the patients assessed the incidence of the signs and symptoms of MPD, including: mouth opening in mm., crepitation, deviation of jaw on opening or closing, and tenderness of muscles of mastication to palpation.

Major Findings: The initial study compared illness behavior of two groups of patients with oro-facial pain; MPD patients and another group of patients with painful, Recurrent Aphthous Stomatitis (RAS). The results of this study showed that the MPD and RAS patients scored similarly on all scales of the IBQ except for the Disease Conviction scale. This suggests that MPD patients are less likely to accept that they do not have a serious illness despite reassurance from the clinician.

Significance to Biomedical Research and the Program of the Institute: Recent studies have suggested that factors other than clinical signs and symptoms are important in determining whether an individual seeks treatment for MPD. Psychosocial concepts such as illness behavior and the tendency for an individual to assume the sick role appear to be more useful for assessing MPD patients than such personality variables as anxiety. A better understanding of the psychological and psychosocial factors associated with pain syndromes such as MPD will be important in successfully treating these patients.

Proposed Course: Future studies will further assess the relationships between attitudes towards illness and the incidence of clinical signs and symptoms in MPD, RAS, and other chronic pain patients.

2. Publications:

Sharav, Y., McGrath, P.A. and Dubner, R.: Masseter inhibitory periods and sensations evoked by electrical tooth pulp stimulation in patients with oral-facial pain and mandibular dysfunction. Arch. Oral Biol., in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00276-03 NA
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Narcotic and Brain Stimulation Analgesia and Human Chronic and Experimental Pain		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Gracely, R.H. Dubner, R. Dionne, R.A. Hoffert, M.J. Wirdzek, P.R. Wolskee, P.J.	Research Psychologist Chief, NAB Staff Fellow Senior Staff Fellow Clinical Nurse Psychologist	NIDR NA NIDR NA NIDR NA NIDR NA NIDR NA NIDR NA
COOPERATING UNITS (if any)		
Dr. Richard Greenberg Division of Neurosurgery Virginia Commonwealth Univ. Richmond, Virginia	Dr. Bruce Smoller Psychiatric Consultant 4400 East-West Highway Bethesda, Maryland	
LAB/BRANCH Neurobiology and Anesthesiology Branch		
SECTION Clinical Pain Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 2.05	PROFESSIONAL: .75	OTHER: 1.30
CHECK APPROPRIATE BOX(ES)		
<input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) The purposes of the study are (1) Assess the effectiveness of <u>chronic electrical stimulation of midbrain sites</u> for the relief of chronic pain in humans; (2) Evaluate the <u>efficacy and mechanisms of traditional narcotic analgesia</u> and compare these to chronic electrical stimulation of midbrain sites; (3) Validate <u>experimental models of pain</u> and their potential diagnostic use in chronic pain patients; and (4) Determine and compare the <u>impact of both traditional narcotic and chronic electrical stimulation therapies on the functional, intellectual and emotional well being</u> of these patients. Participants in this study will be (1) chronic pain patients receiving surgically implanted stimulating electrodes for pain control; (2) chronic pain patients maintained on traditional narcotic analgesics who will not receive implanted stimulating electrodes; and (3) healthy normal volunteers. The effects of chronic brain stimulation in surgical patients will be compared to the effects of narcotics previously administered to patients and to effects of narcotic regimes in nonsurgical chronic pain patients. In addition, the effects of narcotics on perceptual and neural mechanisms of experimentally induced pain and on normal psychological functioning will be <u>compared between chronic patients and normal volunteers free of chronic pain.</u>		

1. Project Description

Objectives: These studies will assess both the mechanisms and relative efficacy of brain stimulation and narcotic analgesics for the control of chronic, intractable human pain. Stimulation of midbrain sites is a recent analgesic technique performed by a small number of neurosurgeons. The present studies address several issues pertinent to the use of this method. How does brain stimulation compare to conventional narcotic administration in terms of: (1) magnitude of analgesia, (2) mechanisms of analgesia, (3) adverse side effects, and (4) tolerance?

Methods Employed: Patients scheduled to receive implants are admitted to the NIH Clinical Center before and after surgery for extensive testing including neurological workups, psychiatric and psychological evaluation, appropriate laboratory tests, clinical pain questionnaires, responses to noxious tooth pulp and heat stimulation, and tests of cognitive and psychomotor functioning. Most patients are assessed before and after administration of analgesics, placebos, narcotic antagonists or brain stimulation. Patients not receiving implanted electrodes and normal volunteers are assessed in a similar manner.

Major Findings: Fifteen patients were assessed during this year. Six were evaluated in a two week preoperative program. Of these, one was not a surgical candidate and two were started on respective trials of tricyclic antidepressants and epidural steroid injections. The remaining three were candidates for electrode implants. Two have received implants but have not returned to NIH for reevaluation. One patient receiving an electrode last year was reevaluated this year. Her pain was controlled completely by infrequent stimulation and she presented no pain on admission. The remaining 9 patients were evaluated in a three day preliminary screening program. Of these, seven were rejected from further study for reasons of heavy drug dependence, poor psychophysical ability, organicity and psychiatric problems. Two may be readmitted for a weaning program to diminish their drug dependence.

Histamine was administered as an active placebo agent to two patients. Both showed altered clinical and experimental pain responses similar to those found after administration of morphine.

A final study presented repetitive painful thermal stimuli to chronic pain patients to assess the differential effect of morphine and placebo on sensations mediated by A-delta and C fiber primary afferent activity. Patients pressed a button to indicate when or if each stimulus was painful. Because of peripheral suppression of A-delta activity by repeated stimulation, sensations to the earlier stimuli in the train are mediated by A-delta fibers and sensations to later stimuli are mediated

by C fibers. Morphine significantly reduced the number of later stimuli rated as painful.

Significance to Biomedical Research and the Program of the Institute: Conservative inclusion criteria reduced the proportion of patients receiving electrodes. Two patients received implants, but they have not been reevaluated. Reevaluation of one patient receiving an electrode in the previous year indicates that infrequent stimulation of less than once-weekly produces long-term analgesia. This result is not consistent with the short-term effect requiring daily stimulation reported by other investigators.

Results of repetitive thermal stimuli presentation suggest that morphine primarily effects pain sensations mediated by C fiber primary afferents. The dull, diffuse pain produced by C fibers is hypothesized to be a major component of chronic pain states. Unlike other experimental pain methods, the repetitive stimulation method separately assesses the activity of C fibers and central summation mechanisms of C fiber pain. These results support the utility of this method for the analysis of neural mechanisms of pain and analgesia.

Proposed Course: Assessment of patients scheduled to receive electrode implants will continue with an anticipated load of 20 patients yearly. Special emphasis will be placed on selecting patients with pain syndromes, such as low back pain, that have been treated successfully by this procedure by other investigators. Histamine will be used routinely as an active placebo agent for patients showing a morphine response and no counterindications of histamine administration.

Studies using noxious thermal stimuli will continue. The differential effects of morphine on A-delta and C fiber activity will be assessed in both chronic pain patients and pain-free volunteers. These studies will assess if pain chronicity alters C fiber summation mechanisms and assess the interaction of morphine and pain chronicity on these mechanisms.

2. Publications:

None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00286-02 NA
PERIOD COVERED October 1, 1980 to September 30, 1981		
CT 0060133		
TITLE OF PROJECT (80 characters or less) Evaluation of Etidocaine and Flurbiprofen for Inhibition of Post-Operative Pain		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Dionne, R.A. Wirdzek, P.R. Sisk, A.L. Gracely, R.	Staff Fellow Clinical Nurse Sr. Asst. Dental Surgeon Research Psychologist	NIDR NA NIDR NA NIDR NA NIDR NA
COOPERATING UNITS (if any)		
LAB/BRANCH Neurobiology and Anesthesiology Branch		
SECTION Clinical Pain Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 1.90	PROFESSIONAL: .90	OTHER: 1.0
CHECK APPROPRIATE BOX(ES)		
<input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords)		
<p> The project consists of studies (1) to evaluate the efficacy of two novel therapeutic agents, alone and in combination, (2) to further document the clinical advantage of <u>preoperative administration of non-steroidal anti-inflammatory analgesics</u> for inhibiting postoperative pain and (3) to <u>compare new analgesic assessment methods</u> to existing analytical techniques. The <u>analgesic activity of flurbiprofen</u> given preoperatively and 4 hours later is being compared to the analgesic effect of acetaminophen. Flurbiprofen pre-treatment is also being compared to administration of a narcotic-mild analgesic combination, oxycodone plus acetaminophen. The anesthetic potency of a <u>long-acting local anesthetic, etidocaine</u>, is being compared to that of lidocaine. Flurbiprofen and etidocaine in combination will be compared to oxycodone plus acetaminophen and lidocaine. These investigations are also evaluating the sensitivity of newly developed scales for measuring analgesic activity in dental outpatients. </p>		

1. Project Description:

The project is a four part factorial comparison of two new therapeutic agents, flurbiprofen and etidocaine, alone and in combination, to standard agents. Flurbiprofen was first compared to acetaminophen to establish analgesic activity in our model and to confirm the sensitivity of the methodology being employed. Flurbiprofen was then compared to one of the more potent analgesic combinations used in dental outpatients, oxycodone plus acetaminophen. A parallel investigation is comparing etidocaine, a new long acting local anesthetic, to lidocaine, the prototype of the amide type local anesthetics. If these investigations are successful in demonstrating a therapeutic advantage, or therapeutic equivalence with reduced toxicity, a fourth investigation will compare flurbiprofen and etidocaine to oxycodone plus acetaminophen and lidocaine.

These investigations extend two previous investigations on the efficacy of preoperative administration of a non-steroidal anti-inflammatory analgesic such as flurbiprofen. These previous investigations have indicated that a significant inhibition of postoperative pain can be achieved by administering such a drug prior to surgery and that less side effects are encountered than if a standard narcotic analgesic combination is administered postoperatively.

Objectives: These investigations are evaluating the analgesic efficacy of flurbiprofen relative to two standard analgesics. A new local anesthetic, etidocaine HCl, is being evaluated for efficacy as a local anesthetic and for the ability to inhibit postoperative pain. These investigations are also evaluating the efficacy of pretreatment with a non-steroidal anti-inflammatory analgesic relative to standard treatment and the efficacy of long-acting local anesthetics for inhibiting postoperative pain. In addition, the sensitivity of novel scales for the measurement of pain, differential descriptor scales and verbal descriptor scales, are being compared to traditional analgesic scales.

Methods Employed: A within-subject, double-blind crossover design is being employed in these investigations. Patients in need of bilateral extraction of impacted third molars serve as subjects. Subjects receive one of the two treatments on a random basis at the first appointment and the alternative treatment is administered at a second appointment, approximately two weeks later. An upper and lower third molar on the same side extracted at each appointment in the usual clinical fashion. Diazepam is administered intravenously prior to and during surgery as a sedative agent up to a maximum of 20 mg.

In the first analgesic study, subjects received either 50 mg of flurbiprofen or 1000 mg of acetaminophen 30 minutes prior to surgery and 4 hours after the initial dose. Lidocaine 2% was used as the local

anesthetic for both sets of extractions. The second analgesic study consisted of two parts. In the first part, 50 mg of flurbiprofen administered 30 minutes pre-operatively and 4 hours later was compared to 10 mg of oxycodone plus 650 mg of acetaminophen given postoperatively. In the second phase of this study, 100 mg of flurbiprofen given pre- and postoperatively was compared to the oxycodone-acetaminophen combination also given pre- and postoperatively. For the comparison of local anesthetics, either 1.5% etidocaine with 1:200,000 epinephrine or 2% lidocaine with 1:100,000 epinephrine is administered in a standard fashion and the adequacy of the anesthetic block confirmed prior to initiating surgery. In the first anesthetic study, the patients' need for postoperative analgesics as the local anesthetic wore off was treated as a dependent variable and patients received their first dose of analgesic at their request when their pain reached a moderate to severe intensity. This proved to be a confounding variable in the assessment of postoperative pain, so that a second study was conducted in which all subjects received a standard postoperative analgesic three hours after surgery.

For the evaluation of the combination of preoperative analgesic plus long-acting local anesthetic, flurbiprofen or placebo will be administered 30 minutes prior to surgery. The flurbiprofen will then be followed by etidocaine as the local anesthetic while the standard treatment will consist of 2% lidocaine. Postoperatively, the experimental treatment will be a second dose of flurbiprofen and the standard treatment will be 10 mg of oxycodone plus 650 mg of acetaminophen.

Patients rate their pain intensity hourly starting two hours after the initial pretreatment dose and continuing to eight hours after the initial dose. Traditional measures of analgesic activity include ordinal ranking scales (none, slight, moderate or severe pain), a global evaluation scale, and a visual analog scale. Newer measures of analgesia being employed are the verbal descriptor scales and differential descriptor scales previously developed and validated at NIDR. Side effects are also recorded and patients indicate which of the two treatments they preferred at the end of the second appointment.

Major Findings: Preoperative administration of 50 mg of flurbiprofen was demonstrated to result in significantly less postoperative pain than 1000 mg of acetaminophen for all measures of analgesia employed. This represents a genuine therapeutic advantage in that no increase in side effects was noted. This study also demonstrated that use of a within-subject crossover design is sufficiently sensitive to differentiate between active drugs in a sample as small as 20 subjects.

In the second analgesic study, preoperative and postoperative administration of 50 mg of flurbiprofen resulted in significantly less pain than postoperative administration of the oxycodone-acetaminophen combination. In addition, the opioid combination tended to result in a higher incidence of side effects. In the second phase of this study, pre- and postoperative administration of 100 mg of flurbiprofen resulted

in significantly less pain than did the opioid combination given on the same schedule. In both phases of this study patients expressed a clear preference for the flurbiprofen over the opioid combination.

In our initial evaluation of the long-acting local anesthetic, etidocaine, the therapeutic effect on postoperative pain was confounded by the variable patient use of analgesics. Preliminary results of the revised study suggest that etidocaine is suppressing pain during the first seven hours following surgery. In addition, the vast majority of patients evaluated to date indicated that, overall, they experienced less postoperative pain following etidocaine than following standard treatment.

The novel scales of analgesic being employed in these studies have shown advantage in comparison to traditional measures. When the difference between treatments has been robust, all the measures of analgesia have demonstrated the effect. However, in one instance where the difference between treatments was subtle, the differential descriptor scale showed a significant difference, not detectable by other traditional analgesic scales. If replicated in other studies, the differential descriptor scale may be a useful tool for assessing pain-relieving drugs such as analgesics and anesthetics in situations where traditional scales lack sensitivity.

Significance to Biomedical Research and the Program of the Institute: The NIDR has played a prominent role in the development of pain control modalities for use in dental outpatients. General anesthesia and related sedative techniques have received most attention in past research. These techniques require extensive training to be used clinically and studies conducted at NIDR indicate that they can result in cardiovascular and respiratory depression. The studies being conducted in this project are aimed at assessing and developing novel methods of controlling pain associated with outpatient dental therapy that do not require extensive training or cause an inordinate risk for the patients. Successful completion of these studies may result in novel methods for controlling pain in dental outpatients. Utilization of such pain control modalities will facilitate the delivery of dental care and, hence, ultimately improve oral health.

Proposed Course: The results of these studies suggest that both flurbiprofen and etidocaine are resulting in a significant reduction in postoperative pain when compared to standard treatment. These two treatments will be administered concurrently to determine if an additive effect can be seen on postoperative pain and to determine if the moderate to severe pain normally associated with painful dental therapy can be markedly reduced or eliminated.

2. Publications:

None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00313-01 NA						
PERIOD COVERED October 1, 1980 to September 30, 1981								
TITLE OF PROJECT (80 characters or less) Conjoint Measurement Analysis of Sensations Evoked by Electrical Tooth Pulp Stimulation								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%;"> <tr> <td style="width: 33%;">Heft, M.W.</td> <td style="width: 33%;">Postdoctoral Fellow</td> <td style="width: 33%;">NIDR NA</td> </tr> <tr> <td>Gracely, R.H.</td> <td>Research Psychologist</td> <td>NIDR NA</td> </tr> </table>			Heft, M.W.	Postdoctoral Fellow	NIDR NA	Gracely, R.H.	Research Psychologist	NIDR NA
Heft, M.W.	Postdoctoral Fellow	NIDR NA						
Gracely, R.H.	Research Psychologist	NIDR NA						
COOPERATING UNITS (if any)								
LAB/BRANCH Neurobiology and Anesthesiology Branch								
SECTION Clinical Pain Section								
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205								
TOTAL MANYEARS: .50	PROFESSIONAL: .50	OTHER:						
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) The objectives of this study are to compare <u>sensory scales</u> developed in a simple <u>magnitude estimation</u> experiment of individual stimuli with a more complex magnitude estimation experiment which requires comparative judgments of relations between stimulus pairs. Subjects make numerical judgments of sensations associated with <u>electrical tooth pulp stimulation</u> . In one case, they estimate the difference between two sensations induced by stimulation of two different incisor teeth; in the other, they estimate the magnitude of sensations induced by stimulation of one incisor. The difference judgments were analyzed by <u>Conjoint Measurement analysis</u> ; a scaling technique which tests for underlying additive structure before determining the sensory scales. In the magnitude estimation experiment of individual stimuli, the geometric mean responses for each current level are assumed to be ratio scales of sensory magnitude. Single-stimulus estimates reliably followed Stevens' power function law with an exponent greater than one, as is common with electrical stimulation of skin. Difference estimates seemed to be based on shallower psychophysical functions than those derived from the single-stimulus estimates, consistent with results from other perceptual continua.								

1. Project Description

Objectives: In magnitude estimation experiments of sensations produced by individual stimuli, subjects rate the magnitude of the sensations produced by randomly presented stimuli with numbers, such that the ratio of a pair of numbers reflects the ratio of the associated sensations. The mean judgments of each stimulus level comprise the sensory scale. Typically, the relationship between the physical stimuli and the numerical judgments, the psychophysical law, are described by Stevens' power function.

Magnitude estimation procedures are also useful in stimulus integration experiments. For example, in a stimulus integration experiment subjects could be asked to make comparative judgments (e.g., differences, sums, or similarities) between levels of two independent stimuli with numbers, again, such that the ratio of a pair of numbers reflects the ratio of perceptual difference, sum, or similarity. The results of such an experiment should give insight into the psychological law (how are subjects making comparative judgments?) in addition to the psychophysical law relating the numerical judgments and the stimulus intensities. These procedures should first include testable criteria that determine how subjects are making comparative judgments before determining the scale values.

Conjoint Measurement analysis is an indirect scaling method which just considers the ranking of the subjective judgments rather than the numerical estimates themselves in order to: 1) test for the presence of an underlying mathematical structure that describes the integration process used by the subjects, and 2) if one exists, determine the sensory scales which satisfy the ranking of the subject's data.

The purpose of the present study is to compare the sensory scales for the electrical tooth pulp stimulation determined by the direct determination of sensory scales in the magnitude estimation experiment of single stimuli with the indirect determination of sensory scales in the Conjoint Measurement analysis of comparative judgments between pairs of stimuli.

Methods Employed: Subjects made numerical judgments of sensations associated with electrical stimulation of the tooth pulp. In one case, they estimated the difference between two sensations induced by stimulation of two different teeth; in the other, they estimated the magnitude of sensation induced by stimulation of one incisor tooth. The difference estimates were analyzed using Conjoint Measurement analysis. Geometric means of numerical estimates of sensations associated with each current level were assumed to be ratio scales of sensation magnitude in the other scaling procedure.

Major Findings: In both scaling procedures the relationships between the sensory scales and the physical stimuli (current levels) were well-described by power functions. The exponents from the Conjoint Measurement analysis of difference estimates varied from .026 to 5.49 and for magnitude estimation varied from 2.42 to 8.31. In almost all instances the slopes determined from the Conjoint Measurement analysis were less than the slopes determined by the direct estimation of the sensory scales, consistent with findings in other sensory systems.

Significance to Biomedical Research and the Project of the Institute: The results provide additional evidence that exponents for power functions which relate physical stimuli and the sensations they produce are different when determined in different experimental paradigms. Further studies are needed to determine whether these differences are related to cognitive strategies used in the two different tasks or to scaling biases associated magnitude estimation procedures.

Proposed Course: Future studies will employ the Conjoint Measurement analysis in studies in which subjects will make comparative judgments between physical stimuli and several classes of cognitive stimuli, e.g., words and numerical categories. Results from these experiments will give insight into how subjects judge: 1) graded physical stimuli and 2) words (or numerical categories) which represent their perceptions of graded stimuli.

2. Publications

None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00314-01 NA						
PERIOD COVERED October 1, 1980 to September 30, 1981								
TITLE OF PROJECT (80 characters or less) Effect of morphine on experimental and clinical pain								
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 40%;">Wolskee, P.J.</td> <td style="width: 40%;">Psychologist</td> <td style="width: 20%;">NIDR NA</td> </tr> <tr> <td>Gracely, R.H.</td> <td>Research Psychologist</td> <td>NIDR NA</td> </tr> </table>			Wolskee, P.J.	Psychologist	NIDR NA	Gracely, R.H.	Research Psychologist	NIDR NA
Wolskee, P.J.	Psychologist	NIDR NA						
Gracely, R.H.	Research Psychologist	NIDR NA						
COOPERATING UNITS (if any)								
LAB/BRANCH Neurobiology and Anesthesiology Branch								
SECTION Clinical Pain Section								
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205								
TOTAL MANYEARS: .60	PROFESSIONAL: .10	OTHER: .50						
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS								
SUMMARY OF WORK (200 words or less - underline keywords) The purposes of this study are: 1) to determine the effect of <u>morphine</u> on the psychophysical judgments of sensory intensity and unpleasantness responses to <u>clinical</u> and <u>experimental pain</u> in normal subjects and chronic pain patients and 2) to determine the validity of experimental pain models by comparison of experimental and clinical pain responses.								

1. Project Description

Objectives: The purpose of these studies is to develop an experimental model to evaluate pharmacological and non-pharmacological pain control methods. The present studies assess experimental and clinical pain responses in both chronic pain patients and normal volunteers. The issue of similarity of response between the 2 groups is addressed.

Methods Employed: Normal volunteers and chronic pain patients assess noxious thermal stimuli by cross modality matching techniques and verbal descriptor scaling. Clinical pain is assessed by seven different pain questionnaires. Two of these questionnaires are recently developed and are being validated in these studies. Subjects are evaluated both before and after the double blind administration of morphine, fentanyl, saline, histamine, or naloxone.

Major Findings: The study compared the effects of morphine in normal pain-free subjects to the effects observed previously for chronic pain patients. Normal subjects scaled noxious thermal stimuli between 45 and 51 degrees centigrade presented to the volar surface of the forearm both before and after the double blind administration of morphine (0.11 mg/kg) or saline placebo. Following morphine administration, verbal descriptor responses of sensory intensity and unpleasantness were reduced in the normal subjects in comparison to placebo. Handgrip measures were not significantly reduced by morphine in comparison to placebo.

An additional study correlated experimental pain response with clinical pain response before and after morphine administration in a group of patients with chronic pain of varying etiology. Five drug-free patients assessed the sensory intensity and unpleasantness of thermocutaneous stimuli (46-51°C) in separate sessions before and after the double blind intravenous administration of morphine or saline placebo. Subjects also completed 7 clinical pain questionnaires in each session. Morphine significantly reduced responses to both the experimentally induced pain sensations and the clinical measures in comparison to placebo.

Significance to Biomedical Research and the Program of the Institute: Morphine significantly reduced the verbal descriptor measures of sensory intensity and unpleasantness in comparison to placebo in normal pain-free subjects. The handgrip responses were not significantly altered by morphine administration. Thus chronic pain patients and pain-free subjects both show decreases in sensory intensity and unpleasantness responses after morphine administration despite observed differences in pain thresholds and unpleasantness ratings of thermal stimuli. These results suggest that the verbal descriptor assessment of thermal pain may provide a model useful for the assessment of pharmacological methods of pain control.

The agreement between the clinical and experimental pain effects of morphine administration also support the validity of verbal scales of contact heat for the experimental assessment of pain control methods. The agreement of the recently developed differential descriptor scales and verbal descriptor check list with the commonly used visual analog scales and McGill pain questionnaire supports their use in the measurement of clinical pain.

Proposed Course: Due to the insignificant results of handgrip in the morphine study, a further experiment will assess if the stimulus range accounted for the lack of positive findings using handgrip as a response measure. Subjects will rate thermal stimuli before and after the double blind administration of fentanyl or placebo. Subjects in one group will determine their own pain range (threshold-tolerance) while the control groups will receive stimuli in the 45-51^oC range as in the previously reported experiment. This will determine the interaction of narcotic administration and stimulus range in this scaling task using handgrip force as a response measure. A further study will use an active placebo to assess the effect of detecting a drug in both groups of subjects.

2. Publications:

None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00020-16 NA															
PERIOD COVERED <p style="text-align: center;">October 1, 1980 to September 30, 1981</p>																	
TITLE OF PROJECT (80 characters or less) Anatomical studies of the trigeminal sensory nuclei and the spinal dorsal horn																	
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Gobel, S.</td> <td style="width: 33%;">Chief, NEA Section</td> <td style="width: 33%;">NIDR NA</td> </tr> <tr> <td>Arvidsson, J.</td> <td>Visiting Fellow</td> <td>NIDR NA</td> </tr> <tr> <td>Sugimoto, T.</td> <td>Visiting Fellow</td> <td>NIDR NA</td> </tr> <tr> <td>Humphrey, E.L.</td> <td>Bio. Lab. Tech. (Ele. Mic)</td> <td>NIDR NA</td> </tr> <tr> <td>Allen, B.M.</td> <td>Biologist</td> <td>NIDR NA</td> </tr> </table>			Gobel, S.	Chief, NEA Section	NIDR NA	Arvidsson, J.	Visiting Fellow	NIDR NA	Sugimoto, T.	Visiting Fellow	NIDR NA	Humphrey, E.L.	Bio. Lab. Tech. (Ele. Mic)	NIDR NA	Allen, B.M.	Biologist	NIDR NA
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COOPERATING UNITS (if any)																	
LAB/BRANCH <p style="text-align: center;">Neurobiology and Anesthesiology Branch</p>																	
SECTION <p style="text-align: center;">Neurocytology and Experimental Anatomy Section</p>																	
INSTITUTE AND LOCATION <p style="text-align: center;">NIDR, NIH, Bethesda, Maryland 20205</p>																	
TOTAL MANYEARS: <p style="text-align: center;">3.15</p>	PROFESSIONAL: <p style="text-align: center;">1.50</p>	OTHER: <p style="text-align: center;">1.65</p>															
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div style="width: 30%;"> <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS </div> <div style="width: 30%;"> <input type="checkbox"/> (b) HUMAN TISSUES </div> <div style="width: 30%;"> <input checked="" type="checkbox"/> (c) NEITHER </div> </div>																	
SUMMARY OF WORK (200 words or less - underline keywords) This project examines the <u>synaptic connections</u> between primary neurons which make up <u>trigeminal and spinal nerves</u> on one hand and the neurons of the medullary and spinal <u>dorsal horns</u> on the other hand especially those in the <u>substantia gelatinosa</u> of Rolando. This project also considers the form, synaptic connections and function of the neurons of the dorsal horn as well as their pathological responses to <u>peripheral nerve injuries</u> . These studies employ <u>electron microscopy</u> , the <u>Golgi method</u> , <u>degeneration techniques</u> and the use of <u>intraneuronal markers</u> such as horseradish peroxidase. The goals of these studies are to delineate trigeminal and spinal <u>pain-temperature pathways</u> and to broaden our understanding of <u>oral-facial sensation</u> .																	

1. Project Description:

Objectives: During the past year our anatomical studies have had three major objectives. First, to examine the morphology and synaptic connections of the axons of those primary neurons which arborize in lamina I of the dorsal horn. Second, to continue the examination of the synaptic connections of several neuronal cell types which comprise the neuropil of the substantia gelatinosa of Rolando (laminae I and II). Third, to begin a series of anatomical studies which seek to examine the pathological effects of peripheral nerve injuries on the injured primary neurons themselves and on the neurons of the dorsal horn which have lost their primary inputs as a consequence of the nerve injury.

Methods Employed: (1) In order to visualize the terminal arbors of primary axons in lamina I, dorsal roots were severed and the protein horseradish peroxidase (HRP) was applied to the cut proximal axons and fills out the terminal arbors of the primary axons so that they can be visualized, following the appropriate histochemical reaction, at the light and electron microscopical levels. (2) HRP was iontophoresed into single dorsal horn neurons using micropipettes and spreads into the axonal and dendritic arbors of the impaled neurons. Having individual neurons filled with HRP allows for detailed electron microscopical analyses of the synaptic inputs that these neurons receive from primary axons and descending aminergic axons. (3) In order to determine the segmental central termination sites and laminar distribution of the primary neurons which comprise the superficial radial nerve, HRP was applied to the proximal cut end of the nerve. The HRP is then transported within the peripheral branches of the nerve to the C₆-C₈ dorsal root ganglia. There it is deposited in the primary cell bodies whose axons comprise this nerve. The HRP is also transported into the central branches of these primary neurons where it marks out the laminar distribution of the primary axons in the dorsal horn of the cervical spinal cord. This same approach was used in experiments in which HRP was applied to superficial radial nerves which had been severed 30 days earlier in order to determine if such injuries might result in the death of primary neurons. (4) HRP was applied to the cut peripheral ends of primary trigeminal neurons inside pulp chambers. In these experiments the HRP was taken up by primary trigeminal neurons, transported intracellularly to their cell bodies in the trigeminal ganglion and then into their terminal axonal arbors in the central nervous system. Having these primary tooth pulp neurons filled with HRP provided an opportunity to study their central termination sites with far greater accuracy than ever before possible.

Major Findings:

1. Primary Axon Studies

One of the most important questions relating to neural circuitry in the dorsal horn concerns the identification of the termination sites of

the many different kinds of primary neurons which subserve the different modalities of somatic sensation. The identification of those primary axons which terminate in lamina I are especially important to our understanding of pain perception because the neurons in lamina I are one of the two major groups of neurons in the dorsal horn which receive nociceptive inputs and convey these inputs to higher centers in the brain. Following the application of HRP to severed dorsal roots, two morphologically distinct kinds of primary axons were discovered. One of these generates many ultrafine endings along unbranched, long rostro-caudally oriented, strand-like collaterals which arise from thin parent branches in Lissauer's tract. In view of these thin parent branches ($\sim 0.3-0.5 \mu\text{m}$ in diameter) these ultrafine primary axons are considered to be unmyelinated (C) primary axons. The second kind of primary axon generates large caliber endings on branched collaterals. These arise from relatively thick parent branches ($\sim 1.0-1.5 \mu\text{m}$ in diameter) in Lissauer's tract which on the basis of their size are considered to be myelinated (A δ) primary axons.

The scalloped endings of both kinds of primary axons lie in the interior of glomeruli where they form axodendritic synapses on small dendritic shafts and spines. It is at these synapses that these two kinds of primary axons are thought to transfer nociceptive and thermal inputs directly to the dendritic arbors of lamina I neurons. Transmitter release at these axodendritic synapses in response to primary inputs can be modified, i.e., probably diminished or inhibited, by synaptic events within the glomeruli from at least three sources. Synaptic vesicle-containing dendrites form dendroaxonic synapses on primary endings and two kinds of axons form axoaxonic synapses either on primary endings or on the intervaricose segments of the primary axons.

2. EM analyses of HRP-filled dorsal horn neurons

The development of techniques in our laboratory for impaling neurons in the dorsal horn with microelectrodes and filling them with HRP (see Z01 DE 00247) has provided a unique opportunity to study their synaptic connections in great detail and gain new insights into their functional roles. During the first year of this study, the two most common cell types of lamina IIa were shown to have very different synaptic connections. The stalked cell received inputs on its dendrites at axodendritic synapses. The IIa islet cell, in addition to receiving inputs at axodendritic synapses, also contained aggregates of synaptic vesicles in its dendrites that were sources of input at dendrodendritic and dendroaxonic synapses.

During this past year, the synaptic connections of a lamina I smooth pyramid, a lamina IV cell and several lamina IIb islet cells which were intracellularly filled with HRP were examined. The lamina I smooth pyramid did not contain synaptic vesicles in its dendrites, received numerous synapses on its cell body and dendrites from dome-shaped axonal endings (D1 and D2 endings) which were identified as descending serotonergic endings in earlier studies (see Z01 DE 00288).

The cell also gave off axon collaterals in lamina I whose endings synapse on other lamina I cell bodies and dendrites. The most impressive feature of the lamina IV cell was its dorsally directed dendrites which entered laminae I and II as well as Lissauer's tract. In these locations it received numerous synaptic contacts from small axonal endings which resembled D1 and D2 serotonergic endings but did not enter glomeruli. These observations suggest that many of the neurons in the deeper laminae of the dorsal horn which send some of their dendrites dorsally into laminae I and II may receive appreciable input from descending aminergic axons on these dorsal dendrites but very little input from the primary axons which arborize in these laminae. The IIb islet cells, like their counterparts in lamina IIa, contained aggregates of synaptic vesicles in their dendrites and formed dendrodendritic synapses on neighboring dendrites within and outside of glomeruli. The IIb islet cell received the fewest synapses from D1 endings of any of the cell types thus far examined.

3. Peripheral Nerve Injury Studies

One of the most important findings of our earlier tooth pulp studies was the observation that dendrites of many neurons in laminae I and II in the medullary dorsal horn exhibited degenerative changes following the loss of primary inputs. This past year a series of experiments was begun in order to examine in a more systematic way the effects of nerve injuries on primary neurons themselves and on the neurons in the dorsal horn that are linked to them synaptically. Following the application of HRP to the superficial radial nerve on one side which had been cut thirty days earlier and to the same uncut control nerve on the other side, similar numbers of HRP-filled cell bodies were found in the C₆-C₈ dorsal root ganglia on both sides. In addition, the density and laminar distribution of the terminal axonal projection was similar on both sides of the C₆-C₈ spinal cord segments. These findings suggest that few if any primary neurons die as a result of the injury. However, many of the primary endings in laminae II and III show a severe loss of their agranular synaptic vesicles which suggests that neural transmission between the injured primary neurons and the dorsal horn neurons may be lacking or markedly reduced. Another important sign of the loss of neural transmission are the appearance of numerous small cavities in the dendrites of lamina II and III neurons. These cavities are similar to those found following tooth pulp extirpations and indicate transsynaptic degeneration in these dorsal horn neurons.

4. Studies of Primary Trigeminal Neurons Innervating Tooth Pulp

The studies begun with Dr. Arvidsson last year concerning the identification of the central termination sites of those primary neurons which innervate tooth pulps were completed this past year. Two major sites were identified. One consists of a long continuous column which extends from the main sensory nucleus at its rostral limit through subnuclei oralis and interpolaris into lamina V in the medullary dorsal

horn at its caudal limit. This column is situated dorsomedially within each of these structures. The second termination site is found in the dorsomedial parts of laminae I and IIa in the medullary dorsal horn. During the past year, a manuscript was prepared and submitted for publication detailing these findings along with the identification of the central termination sites of the primary neurons which make up the inferior alveolar nerve.

Significance to Biomedical Research and the Program of the Institute: The rationale for utilizing orofacial pain in diagnosing dental pathology, for providing anesthesia for dental procedures and for understanding the role of pain in reflex movement of the musculature of the head and neck is based on our knowledge of orofacial pain pathways. Our knowledge of much of these neural pathways today remains fragmentary. Our neuro-anatomical studies are aimed at establishing a more definitive circuit diagram of trigeminal, as well as spinal, pain pathways.

The trigeminal nerve is involved in a host of chronic pain states which include trigeminal neuralgia (tic douloureux), glossodynia (burning tongue) and other facial neuralgias. Explanations of these pain states usually involve mechanisms related to pathology of the peripheral nerve. However many of the symptoms of tic douloureux, for example, cannot be explained without considering synaptic circuitry in the central nervous system. Why do the most innocuous stimuli trigger the pain episode? Is the loss of teeth somehow involved in a disruption of synaptic connections in the spinal trigeminal nucleus? Our peripheral nerve injury studies seek to determine whether transsynaptic degenerative changes in dorsal horn neurons consequent to the loss of primary inputs play a crucial role.

Recent technical advances have made it possible to selectively study individual neurons in pain pathways at the light and electron microscopical levels. Data from such studies will provide more detailed information about the neural circuitry of trigeminal pain pathways and will permit us to design more critical experiments to approach the above as well as other questions concerning chronic pain states in the orofacial region.

Proposed Course: During the coming year, four lines of experimentation are planned. First we will continue our investigation of the morphology and synaptic connections of primary axons, especially those in lamina II. Experiments will be carried out to determine the sources of those axonal endings and synaptic vesicle-containing dendrites which establish synaptic connections with and thereby regulate transmitter release from the primary axons. Second, we will continue our studies of the morphology and synaptic connections of the major cell types of the dorsal horn which have been intracellularly filled with HRP. Our efforts will be concentrated on the different kinds of lamina I neurons and those neurons in laminae III-IV which send some of their dendrites or axonal branches dorsally into lamina I and II. Third, the peripheral

nerve injury studies will be continued in order to try to answer two important questions. (1) What intracellular events take place within the injured primary neurons that affect transmitter release and synaptic transmission? (2) Which neurons in the dorsal horn are damaged by the loss of primary inputs? If several technical impediments relating to specimen preservation can be overcome we will try to resume our developmental studies which seek to define which components of the neural circuitry of the pain pathways in the dorsal horn are already in place at birth and which components develop postnatally.

2. Publications:

Gobel, S., Falls, W.M., Bennett, G.J., Abdelmoumene, M., Hayashi, H. and Humphrey, E.: An EM analysis of the synaptic connections of horseradish peroxidase-filled stalked cells and islet cells in the substantia gelatinosa of adult cat spinal cord. J. Comp. Neurol., 194: 781-807 (1980).

Gobel, S., Hockfield, S. and Ruda, M.A.: An anatomical analysis of the of the similarities between medullary and spinal dorsal horns. In: Oral-Facial Sensory and Motor Functions, edited by Y. Kawamura and R. Dubner, Quintessence, Tokyo, In Press.

Arvidsson, J. and Gobel, S.: An HRP study of the central projections of primary trigeminal neurons which innervate tooth pulps in the cat. Brain Res. 210:1-16 (1981).

Gobel, S., Falls, W.M. and Humphrey, E.: Morphology and synaptic connections of ultrafine primary axons in lamina I of the spinal dorsal horn: Candidates for the terminal axonal arbors of primary neurons with unmyelinated (C) axons. J. Neurosci., in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 DE 00288-02 NA
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (80 characters or less) Neuropharmacological Characterization of Synaptic Circuitry in the Dorsal Horn		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
Ruda, M.A. Gobel, S. Coffield, J.A.	Senior Staff Fellow Chief, NEA Section Biologist	NIDR NA NIDR NA NIDR NA
COOPERATING UNITS (if any)		
LAB/BRANCH Neurobiology and Anesthesiology Branch		
SECTION Neurocytology and Experimental Anatomy Section		
INSTITUTE AND LOCATION NIDR, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 2.65	PROFESSIONAL: 1.05	OTHER: 1.60
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a1) MINORS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) <u>Neurotransmitters</u> were localized to specific populations of axonal endings and neurons in the medullary and spinal <u>dorsal horns</u> using the technique of <u>immunocytochemistry</u> at the <u>light</u> and <u>EM</u> level. Immunocytochemically labeled <u>enkephalinergic</u> (ENK) <u>axonal endings</u> were found to synapse directly on <u>thalamic projection neurons</u> labeled by retrograde transport of horseradish peroxidase. This observation demonstrates that one major site of <u>opiate</u> modulation of <u>noxious input</u> in the dorsal horn occurs directly on projection neurons, indicating that opiates act, at least in part, on post-synaptic receptors located on thalamic projection neurons. Several different morphological types of <u>enkephalinergic neurons</u> were observed in the dorsal horn. Based on the morphology of the dendrites of one type of neuron identified in the immunocytochemical studies, we propose that one class of ENK neurons in the dorsal horn are the <u>lamina IIb islet cells</u> . <u>Serotonergic axonal endings</u> were identified in the dorsal horn. The immunocytochemically labeled profiles are oriented primarily in the rostro-caudal plane and are found in all lamina. Ultrastructurally, most are dome shaped endings which synapse on dendritic shafts and spines.		

1. Project Description:

Objectives: The localization and characterization of neurotransmitters in the dorsal horn forms the basis for understanding the modulation of nociceptive input in pain pathways. The objective of our experiments is twofold: (1) to describe the location and ultrastructural morphology of pharmacologically identified axonal endings and neurons in the medullary (MDH) and spinal (SDH) dorsal horn; (2) to develop a pharmacologically characterized circuit diagram of potential synaptic interactions between dorsal horn neurons and their afferent input.

Methods Employed: With the advent of the immunocytochemical technique new vistas have been opened for studying the pharmacology of the nervous system. We have developed the technique of immunocytochemistry in our laboratory so that it can be used at both the light and electron microscopic level to label populations of neurotransmitter specific neuronal cell bodies, dendrites, axons and axonal endings.

The immunocytochemical technique employs the production of antibodies to a characterized neurotransmitter. The neurotransmitter is subsequently visualized by tagging it with a chromagen. Antibodies to enkephalin (ENK), substance P (SP), somatostatin (SOMA) and cholecystokinin (CCK) are commercially available while that to serotonin (5HT) was the generous gift of Dr. H. Steinbusch and that to dopamine- β -hydroxylase (DBH) was supplied by Dr. D. Jacobowitz.

Normal cats, or those pretreated with colchicine to block axoplasmic transport and thus concentrate the neurotransmitter in the cell soma for visualization, were perfused with 4% paraformaldehyde and 0.2% glutaraldehyde. The tissue was sectioned on a vibratome and incubated in the primary antiserum overnight. Using the unlabeled antibody peroxidase anti-peroxidase immunocytochemical staining method of Sternberger, the neurotransmitter is visualized at the light microscopic level by the presence of red-brown reaction product. Following osmication, the reaction product becomes electron dense and appears as a flocculent black material associated with synaptic vesicles, the outer mitochondrial membrane and other subcellular organelles as well as the cytoplasm itself.

In addition to experiments in which only one component of the neuropil was labeled, two studies are underway which involve the differential labeling of two neuronal components in the same experiment in order to determine potential synaptic interrelationships.

In one experiment, thalamic projection neurons are labeled by retrograde transport of horseradish peroxidase (HRP) after an injection of HRP into the thalamus. Following a survival time of three days, the animals are sacrificed, the tissue sectioned, and reacted with cobalt

chloride intensified diaminobenzidine to produce a black punctate reaction product in the retrogradely labeled neurons. The tissue is subsequently processed for immunocytochemistry to produce red-brown labeled immunoreactive profiles adjacent to the blackened neurons. Following osmication and plastic embedding, the presence of synaptic interactions can be ascertained at the ultrastructural level.

The second double label experiment involves the combination of immunocytochemical labeling of neurotransmitters in tissue sections which contain a physiologically characterized intracellularly stained neuron. The proximity of the immunocytochemically labeled profiles adjacent to the intracellularly filled neuron can be evaluated at the light microscopic level and potentially identified as a synaptic interaction at the ultrastructural level.

Major Findings:

Thalamic Projection Neurons:

Enkephalin, an opiate peptide which may represent one of the natural ligands of opiate receptors, can be localized to several different lamina in the dorsal horn, some of which contain the neuronal somas and dendritic arbors of the thalamic projection neurons. Several studies have shown that ENK mediates inhibition of the response of neurons to noxious stimulation. An understanding of the neural circuitry accessed by ENK is thus critical to the elucidation of the mechanisms of pain and analgesia. By combining the techniques of immunocytochemistry and retrograde transport of HRP we have achieved the first direct anatomical demonstration of a synaptic relationship between axonal endings containing an opiate peptide and an identified post-synaptic neural element in the dorsal horn. Enkephalin immunoreactive axonal endings were shown to make direct synaptic contact with the soma and proximal dendrites of lamina V dorsal horn thalamic projection neurons. This observation demonstrates that one major site of opiate modulation of the transfer of nociceptive information in the dorsal horn is a direct synaptic event on the projection neurons themselves.

Enkephalinergic Neurons in the Dorsal Horn:

In collaboration with Drs. G. Bennett and S. Gobel we have identified one class of ENK containing neurons in the dorsal horn. The ENK neuronal cell type is the lamina IIb islet cell, a Golgi type II interneuron which is a proposed inhibitory interneuron. The identification was made by comparing the light and ultrastructural morphology of an intracellularly stained lamina IIb islet cell with that of immunocytochemically labeled ENK somas and dendrites in lamina IIb. At the light microscopic level the location and orientation of the ENK neurons resembled that of the IIb islet cell. At the ultrastructural level the ENK labeled dendrites contained vesicles and received synapses from large scalloped central endings as do the lamina IIb islet cells. This observation suggests

that one class of ENK neurons in the dorsal horn are local circuit inhibitory interneurons.

Immunocytochemical Localization of Serotonin in the Dorsal Horn:

As a continuation of our studies of monoamines in pain pathways, we have employed the immunocytochemical technique to localize 5HT in the dorsal horn. The immunocytochemical approach has an advantage over the autoradiographic technique employed in previous studies of 5HT in that it allows visualization of the entire 5HT axon which can be followed as it courses through the neuropil. In preliminary observations, it appears that 5HT axons have a decidedly rostro-caudal orientation. Their numbers are greatest in lamina I and decrease in lamina IIa and are lowest in lamina IIb. The immunocytochemical localization has drawn attention to the presence of 5HT in other lamina of the spinal cord. 5HT is found throughout the spinal cord with each lamina varying only in the density of innervation. As in the [3 H]5HT uptake experiments, ultrastructurally, lamina I and II 5HT axonal endings are mainly dome-shaped, forming a single synapse on dendritic shafts and spines.

Immunocytochemical Localization of Norepinephrine in the Dorsal Horn:

The monoamine norepinephrine (NE) has been shown to be involved in the mechanisms of analgesia in the dorsal horn. Earlier studies in our laboratory have localized NE in lamina I and II of the dorsal horn using the technique of autoradiography following uptake of [3 H]NE. In further studies employing antibodies to dopamine- β -hydroxylase, a critical enzyme in the synthesis of NE, we have accurately localized the laminar location of NE axons in the medulla and spinal cord. NE axons are found in the superficial lamina of the dorsal horn as well as lamina V and VI in the neck of the dorsal horn, and in the ventral horn. The density of immunocytochemically labeled NE labeled axons is significantly less than that observed for 5HT suggesting that the monoamine 5HT plays a greater role than NE in the modulation of noxious input in the dorsal horn.

Intracellularly Stained Neurons Combined with Immunocytochemistry:

Four intracellularly HRP-filled neurons, which were subsequently run for immunocytochemical labeling of their afferents, were examined at the electron microscopic level. No synaptic interactions between the two labeled neuronal elements were found. This negative data is most likely due to the technical limitations of the combined techniques. Immunocytochemistry at the electron microscopic level is limited by the penetration of the antibodies into the tissue section. In most cases, only the top 5 μ m of the section is exposed to the antibodies. Since there is no feasible way to control how close to the surface of the tissue the intracellularly filled neuron lies, little of the cell is ever in the field of immunoreactive profiles where a synaptic interaction can be identified. As an alternative approach, in collaboration with Drs. M. Hoffert and V. Miletic, the HRP-filled cells are now being

screened using light microscopic immunocytochemistry which has a penetration of greater than 15 μ into the tissue section. The approach will allow us to determine at the light microscopic level whether a particular class of neurons is more likely to receive input from a given neurotransmitter by the proximity of the immunocytochemically labeled axonal endings to the intracellularly filled neuron. Although technically difficult, this project is important in that synaptic interactions thus identified will provide an unequivocal demonstration of neural circuits.

Significance to Biomedical Research and the Program of the Institute:

Several disease states such as cancer and stroke lead to intractable pain for which adequate therapy is unavailable. In other chronic pain states such as trigeminal neuralgia, the ideology is unknown. Knowledge of the synaptic circuitry is of critical importance in understanding chronic pain states. Our recent technical advances, developed to identify the mechanism of action of these pain states, have allowed visualization of pharmacologically characterized neurons and axonal endings. We are attempting to identify and characterize the pharmacology of the neural circuitry which subserves nociception. Our experiments have provided a circuit diagram of the monoaminergic and peptidergic inputs to layers I and II of the medullary and spinal dorsal horns. The analysis of monoaminergic axonal endings is of particular significance since the activation of descending aminergic pathways are implicated in the mechanisms of analgesia. The study of enkephalinergic neural circuitry furthers our understanding of the role of opiates in pain pathways. Our experiments have identified several important sites of action of neurotransmitters in pain pathways. Future experiments will add to our description of a pharmacologically characterized neural circuit in the dorsal horn. A more thorough knowledge of the synaptic circuitry involved in pain pathways will ultimately help answer questions concerning the mechanisms of chronic pain states and lead to selection of appropriate drug treatments.

Proposed Course: The coming years work will represent a continuation of ongoing experiments using the immunocytochemical technique to localize neurotransmitters in the dorsal horn. Further data collection is needed in our EM analysis of 5HT and NE axonal endings. Upon completion of those studies, an analysis of substance P and somatostatin containing axonal endings will begin.

The double label experiments in which the neurotransmitter employed by afferents to thalamic projection neurons is determined, will be continued in order to look at lamina I projection neurons. The project will be expanded to determine if these same projection neurons which receive ENK input also receive monoaminergic synaptic input.

The last series of experiments will continue to attempt to determine the neurotransmitters of the afferents to the intracellularly stained neurons. It is hoped that the light microscopic analysis of the relationship of immunocytochemically labeled axonal endings to the intracellularly

filled neuron will aid in future selection of material to be used for ultrastructural analysis.

2. Publications:

Ruda, M.A., Allen, B. and Gobel, S.: Ultrastructure of Descending Serotonergic Axonal Endings in Layers I and II of the Dorsal Horn. J. Physiol. (Fr), in press.

Ruda, M.A., Allen, B. and Gobel, S.: Ultrastuctural analysis of medial brainstem afferents to the superficial dorsal horn. Brain Res., 205:175-180, 1981.

Ruda, M.A.: Opiates and Pain Pathways: Demonstration of Enkephalinergic Synapses on Thalamic Projection Neurons in the Dorsal Horn. Science, in press.

PART V

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

CONTRACTS

October 1, 1980 - September 30, 1981

This document was prepared for administrative use at NIH. The comments and declarations of its contributors are their own and do not necessarily represent an official statement of the Institute.

Compiled By

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

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PART VI - INDEXES

IDENTIFICATION NUMBER..... NO1 DE02424-02
ORGANIZATION..... AMERICAN DENTAL ASSOCIATION
ADDRESS..... CHICAGO ILLINOIS
INITIAL START DATE..... 02-01-80
EXPIRATION DATE..... 12-09-82
ORGANIZATION CODE..... 0256501
PROJECT DIRECTOR..... GIFT, HELEN C
NIDR PROJECT OFFICER..... FREW, RALPH A
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: ROLE OF DENTISTS AND PEDIATRICIANS IN USE OF CARIES
PREVENTION METHODS

OBJECTIVES AND WORK SCOPE : Conduct a national survey through a written questionnaire administered to a stratified probability sample of practicing dentists and pediatricians to assess: the extent of knowledge of current caries prevention methods among dental practitioners and pediatricians; the acceptance and use of these procedures among practitioners; the extent to which practicing dentists and pediatricians advise patients regarding caries prevention; and the characteristics of dentists and pediatricians who are aware of and receptive to preventive philosophies.

IDENTIFICATION NUMBER..... NO1 DE02425-03
ORGANIZATION..... ILLINOIS, UNIVERSITY OF, BOARD OF
ADDRESS..... CHICAGO ILLINOIS
INITIAL START DATE..... 06-25-80
EXPIRATION DATE..... 06-24-82
ORGANIZATION CODE..... 0577703
PROJECT DIRECTOR..... KINGHORN, DOUGLAS A
NIDR PROJECT OFFICER..... VARGOSKO, ANDREW J
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: DEVELOPMENT OF NATURALLY OCCURRING, NONCARIOGENIC SWEETENERS

OBJECTIVES AND WORK SCOPE : Identify, isolate, and develop naturally occurring sweeteners which are noncariogenic in humans and may be used as dietary sucrose substitutes. Characterization of their physical and chemical properties will include: determination of melting point; evaluation of purity; determination of stability in the dry state and hygroscopicity; stability and solubility in aqueous solutions of acids and alkalis at various pH levels, temperatures, and time intervals; and stability under a variety of conditions of recovery, storage, and use.

IDENTIFICATION NUMBER..... NO1 DE02426-00
ORGANIZATION..... ALABAMA, UNIVERSITY OF
ADDRESS..... BIRMINGHAM ALABAMA
INITIAL START DATE..... 08-01-80
EXPIRATION DATE..... 07-31-83
ORGANIZATION CODE..... 1288803
PROJECT DIRECTOR..... MICHALEK, SUZANNE
NIDR PROJECT OFFICER..... KLEIN, DAVID L
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: IMMUNIZATION OF RODENTS WITH ANTICARIES VACCINES

OBJECTIVES AND WORK SCOPE : Determine the efficacy and suitability of incorporating minimally toxic non-Freund-type adjuvants into anticaries vaccines. These vaccines will be used to immunize rodents. Antibody responses and immunoglobulin levels will be measured in the serum and saliva of these animals. Following viable cariogenic bacterial challenge, the dental caries that develop will be scored. Histopathological examinations of tissues at the injection sites will also be made. From the many categories of adjuvants currently available, it is anticipated that trials with new formulations will give rise to well-tolerated, minimally toxic preparations which will elicit good titers of protective antibodies.

IDENTIFICATION NUMBER..... NO1 DEO2427-04
ORGANIZATION..... PURDUE RESEARCH FOUNDATION
ADDRESS..... W. LAFAYETTE INDIANA
INITIAL START DATE..... 08-01-80
EXPIRATION DATE..... 08-28-82
ORGANIZATION CODE..... 1481401
PROJECT DIRECTOR..... WHISTLER, ROY
NIDR PROJECT OFFICER..... JOHNSON, SHARON L
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: NONCARIOGENIC SWEETENERS TO BE USED AS DIETARY SUCROSE
SUBSTITUTES

OBJECTIVES AND WORK SCOPE : Synthesize and develop
sweeteners which are noncariogenic in humans and may be used
as dietary sucrose substitutes. Characterization of their
physical and chemical properties will include:
determination of melting point; evaluation of purity;
determination of stability in the dry state and
hygroscopicity; stability and solubility in aqueous
solutions of acids and alkalis at various pH levels,
temperatures, and time intervals; and stability under a
variety of conditions of recovery, storage, and use.

IDENTIFICATION NUMBER..... NO1 DE02428-04
ORGANIZATION..... RESEARCH TRIANGLE INSTITUTE
ADDRESS..... RES TRI PARK NORTH CAROLINA
INITIAL START DATE..... 09-22-80
EXPIRATION DATE..... 09-21-82
ORGANIZATION CODE..... 6939101
PROJECT DIRECTOR..... COOK, CLARENCE E.
NIDR PROJECT OFFICER..... JOHNSON, SHARON L
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: NONCARIOGENIC SWEETENERS TO BE USED AS DIETARY SUCROSE
SUBSTITUTES

OBJECTIVES AND WORK SCOPE : Synthesize and develop
sweeteners which are noncariogenic in humans and may be used
as dietary sucrose substitutes. Characterization of their
physical and chemical properties will include:
determination of melting point; evaluation of purity;
determination of stability in the dry state and
hygroscopicity; stability and solubility in aqueous
solutions of acids and alkalis at various pH levels,
temperatures, and time intervals; and stability under a
variety of conditions of recovery, storage, and use.

IDENTIFICATION NUMBER..... NO1 DEO2429-01
ORGANIZATION..... SOUTHERN RESEARCH INSTITUTE
ADDRESS..... BIRMINGHAM ALABAMA
INITIAL START DATE..... 09-26-80
EXPIRATION DATE..... 09-25-82
ORGANIZATION CODE..... 7657001
PROJECT DIRECTOR..... MYERS, WILLIAM E
NIDR PROJECT OFFICER..... BOWEN, WILLIAM H
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: IMPROVED METHODS OF DELIVERING CARIOSTATIC AGENTS TO
THE ORAL CAVITY

OBJECTIVES AND WORK SCOPE : The Contractor shall develop new techniques of applying cariostatic substances to the mouth to gain improved access and prolonged retention around caries-prone areas. To enhance adherence of capsules to teeth and mucous membranes, the study of modifying capsule surface charges will be given first priority and the effects of tagging capsules with anti-S. mutans IgG second priority. Collaborative animal studies will be conducted after the Contractor supplies NIDR with capsules having acceptable retention and release rates. They will consist of encapsulated sodium fluoride in oxidized starch whose polylyxine altered surfaces will release fluoride at different rates as determined in saliva studies.

IDENTIFICATION NUMBER..... NO1 DE12430-00
ORGANIZATION..... HAZLETON LABORATORIES
ADDRESS..... VIENNA VIRGINIA
INITIAL START DATE..... 07-01-81
EXPIRATION DATE..... 06-30-83
ORGANIZATION CODE..... 9640802
PROJECT DIRECTOR..... DALGARD, DAN W
NIDR PROJECT OFFICER..... DALGARD, DAN W
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: INVESTIGATION OF ANTICARIES VACCINE IN PRIMATES

OBJECTIVES AND WORK SCOPE : This procurement is for veterinary care, quarantine procedures, technical support care, and housing for research animals which are presently part of an investigation in anticaries immunization with subhuman primates. The Contractor will house approximately 70 primates (*Macaca fascicularis*) in accordance with the highest standards of animal husbandry.

IDENTIFICATION NUMBER..... NO1 DE12431-00
ORGANIZATION..... STATE UNIVERSITY OF NEW YORK AT BUF
ADDRESS..... ALBANY NEW YORK
INITIAL START DATE..... 07-01-81
EXPIRATION DATE..... 06-30-82
ORGANIZATION CODE..... 5992614
PROJECT DIRECTOR..... RIPA, LOUIS W
NIDR PROJECT OFFICER..... SWANGO, PHILIP A
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: CLINICAL TRIAL OF COMBINED DENTIFRICE AT DIFFERENT
FLUORIDE CONCENTRATIONS

OBJECTIVES AND WORK SCOPE : A three year longitudinal clinical trial of MFP-NaF dentifrice formulated at different fluoride concentrations. The purposes of this procurement are: to evaluate the anticaries efficacy of a combined MFP-NaF dentifrice with a total fluoride concentration of 1000 ppm; and to determine whether the efficacy of this formulation can be improved by raising the total fluoride concentration to 2500 ppm. A standard MFP dentifrice with a fluoride concentration of 1000 ppm will be used as a positive control. Both experimental formulations will contain NaF and MFP at concentrations equimolar with respect to fluoride.

IDENTIFICATION NUMBER..... NO1 DE12432-00
ORGANIZATION..... COLGATE-PALMOLIVE COMPANY
ADDRESS..... PISCATAWAY NEW JERSEY
INITIAL START DATE..... 06-30-81
EXPIRATION DATE..... 06-29-82
ORGANIZATION CODE..... 1606901
PROJECT DIRECTOR..... MELLBERG, JAMES R
NIDR PROJECT OFFICER..... MILLER, ANN
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: EXAMINATION OF RELATION BETWEEN CARIES AND TOOTH ENAMEL
FLUORIDE

OBJECTIVES AND WORK SCOPE : A research study to establish and/or refine an acid etch biopsy procedure in order to examine whether a relationship exists between the subsurface fluoride content of the enamel and caries experience. Based on a demonstration of the biopsy technique and data obtained in the first phase, an approved biopsy procedure will be carried out in a three month clinical trial with school children.

IDENTIFICATION NUMBER..... NO1 DE12433-00
ORGANIZATION..... MINNESOTA UNIVERSITY OF
ADDRESS..... ST PAUL MINNESOTA
INITIAL START DATE..... 09-01-81
EXPIRATION DATE..... 08-31-82
ORGANIZATION CODE..... 5365601
PROJECT DIRECTOR..... BANDT, CARL
NIDR PROJECT OFFICER..... HOFFELD, J TERRELL
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: MICROSCOPIC EVALUATION OF SUBGINGIVAL PLAQUE IN PATIENTS
WITH PERIODONTAL INFLAMMATION

OBJECTIVES AND WORK SCOPE : Determine the reliability of phase contrast microscopic evaluation of subgingival plaque as a correlate of periodontal inflammatory status; utility of phase contrast microscopic evaluation of subgingival plaque as a diagnostic and prognostic tool; utility of videotape recording of phase contrast microscopic observation of subgingival plaque as a means of patient motivation; and relative efficacy of a combined regimen of flossing, irrigation, and regularly patient-applied hypertonic salts in oxidative antiseptic, compared with a conventional home treatment regimen of flossing and commercial dentifrice in the control of the subgingival flora and periodontal inflammation.

IDENTIFICATION NUMBER..... NO1 DE12434-00
ORGANIZATION..... EASTMAN DENTAL CENTER
ADDRESS..... ROCHESTER NEW YORK
INITIAL START DATE..... 09-28-81
EXPIRATION DATE..... 09-27-83
ORGANIZATION CODE..... 2300901
PROJECT DIRECTOR..... CURZON, M.
NIDR PROJECT OFFICER..... JOHNSON, SHARON L
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: IDENTIFICATION OF CARIOGENIC ELEMENTS OF FOOD

OBJECTIVES AND WORK SCOPE : A research study of the cariogenic potential of common snack foods. The cariogenicity of foods will be assessed by the method in which rats are fed their essential nutrition by gastric intubation, and only the test foods--fed through a programmed feeder--are allowed to come in contact with the animals' teeth. The study will also include salivary function measurements and microbial implantation measurements.

IDENTIFICATION NUMBER..... NO1 DE42434-21
ORGANIZATION..... HAZLETON LABORATORIES
ADDRESS..... VIENNA VIRGINIA
INITIAL START DATE..... 05-01-74
EXPIRATION DATE..... 06-30-81
ORGANIZATION CODE..... 9640802
PROJECT DIRECTOR..... DALGARD, DAN W
NIDR PROJECT OFFICER..... BOWEN, WILLIAM H
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: ANTICARIES IMMUNIZATION IN SUBHUMAN PRIMATES

OBJECTIVES AND WORK SCOPE : The Contractor will provide 40-50 Macaca fascicularis monkeys approximately sixteen months of age. The Contractor would house and maintain the monkeys with suitable sterility and safety procedures for a period of not less than two years. The monkeys would be fed eight times daily and less frequently on weekends with a special caries-conducive diet which would be specified by NIDR. The Contractor would also provide facilities for clinical (general anesthesia and minor oral surgery) and radiographic examinations.

IDENTIFICATION NUMBER..... NO1 DE52452-12
ORGANIZATION..... EMORY UNIVERSITY
ADDRESS..... ATLANTA GEORGIA
INITIAL START DATE..... 05-21-75
EXPIRATION DATE..... 07-31-81
ORGANIZATION CODE..... 2384501
PROJECT DIRECTOR..... MC CLURE, HAROLD M
NIDR PROJECT OFFICER..... HASSELL, JOHN R
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: INDUCTION OF ORAL-FACIAL MALFORMATIONS IN M RHESUS MONKEY

OBJECTIVES AND WORK SCOPE : The Contractor will conduct investigations pertaining to experimental induction of oral-facial malformations in fetal rhesus monkeys; documentation of metabolism of administered drugs in pregnant animals and their fetuses; and chromosomal evaluation of pregnant animals and products of conception, following drug administration. He will establish a breeding colony of rhesus monkeys sufficient to provide 15 pregnancies; establish the menstrual cycles of the females and conduct a breeding program to insure a minimum of 15 timed pregnancies; administer specified compounds to the pregnant animals at various stages of gestation; and monitor effects of drug administration in both pregnant animals and their progeny.

IDENTIFICATION NUMBER..... NO1 DE52456-06
ORGANIZATION..... ALABAMA, UNIVERSITY OF
ADDRESS..... BIRMINGHAM ALABAMA
INITIAL START DATE..... 06-20-75
EXPIRATION DATE..... 10-19-80
ORGANIZATION CODE..... 0556601
PROJECT DIRECTOR..... MC GHEE, JERRY R
NIDR PROJECT OFFICER..... VARGOSKO, ANDREW J
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: SALIVARY IMMUNOGLOBULIN IGA DEFICIENCY IN HUMANS RELATED
TO CARIES

OBJECTIVES AND WORK SCOPE : The Contractor proposes to study a population of more than 25 IgA deficient patients and appropriate controls to correlate the presence or absence of IgA and caries incidence. He will measure salivary immunoglobulins and factors such as lysozyme, lactoferrin, and peroxidase. Plaque will be collected and analyzed for the principal oral bacteria present. Plaque proteins will be studied from the standpoint of in situ function-possible coating and/or aggregation of important plaque bacteria. He will correlate these findings with the clinical picture occurring in these patients, including past and present caries, and gingival and Periodontal Disease indices.

IDENTIFICATION NUMBER..... NO1 DE52478-07
ORGANIZATION..... MICHIGAN, UNIVERSITY OF
ADDRESS..... ANN ARBOR MICHIGAN
INITIAL START DATE..... 06-23-75
EXPIRATION DATE..... 12-31-82
ORGANIZATION CODE..... 5249701
PROJECT DIRECTOR..... MC NAMARA, JAMES A
NIDR PROJECT OFFICER..... CHRISTIANSEN, R L
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: MUSCLE REATTACHMENT AND MIGRATION WITH OR WITHOUT OSSEOUS SURGERY

OBJECTIVES AND WORK SCOPE : This project will provide for studies to determine changes in neuromuscular physiology and craniofacial function due to muscle reattachment, transplantation, and migration with or without osseous surgery, utilizing a young adult primate animal model system to identify and describe stages in muscle adaptation in two types of surgical procedures designed by the Contractor.

IDENTIFICATION NUMBER..... NO1 DE52484-07
ORGANIZATION..... PENNSYLVANIA, UNIVERSITY OF
ADDRESS..... PHILADELPHIA PENNSYLVANIA
INITIAL START DATE..... 06-27-75
EXPIRATION DATE..... 06-30-82
ORGANIZATION CODE..... 6463801
PROJECT DIRECTOR..... YANKELL, SAMUEL L
NIDR PROJECT OFFICER..... SHERN, ROALD J
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: CLINICAL SCREENING OF ANTIPLAQUE AND ANTIMICROBIAL AGENTS

OBJECTIVES AND WORK SCOPE : Clinical testing of potential antiplaque and antimicrobial agents. Agents shall be applied both singly and in combination in vehicles such as mouthrinses and gels in various regimens and durations. Test groups shall not consist of more than 50 subjects. All testing shall be short term, i.e. 1-16 weeks. CORE MEASUREMENTS - plaques extent, dry weight, pH, microflora, gingivitis. ELECTIVE MEASUREMENTS - thickness, biochemistry, cervicular flow photography, pO.

IDENTIFICATION NUMBER..... NO1 DE62491-11
ORGANIZATION..... ALABAMA, UNIVERSITY OF
ADDRESS..... BIRMINGHAM ALABAMA
INITIAL START DATE..... 06-28-76
EXPIRATION DATE..... 03-31-82
ORGANIZATION CODE..... 0556601
PROJECT DIRECTOR..... SHIOTA, T
NIDR PROJECT OFFICER..... VARGOSKO, ANDREW J
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: USE OF MUTANTS OF CARIOGENIC STREPTOCOCCI TO PREVENT
DENTAL CARIES

OBJECTIVES AND WORK SCOPE : The Contractor will select at least one strain from each of at least two different serotypes of S. mutans to conduct a research study on the use of mutants of cariogenic streptococci to prevent dental caries. These strains should produce abundant glucan and should be proven to be cariogenic in rodents.

IDENTIFICATION NUMBER..... NO1 DE62494-06
ORGANIZATION..... VIRGINIA COMMONWEALTH UNIVERSITY
ADDRESS..... RICHMOND VIRGINIA
INITIAL START DATE..... 06-30-76
EXPIRATION DATE..... 12-30-80
ORGANIZATION CODE..... 0353201
PROJECT DIRECTOR..... FREER, RICHARD J
NIDR PROJECT OFFICER..... SCHIFFMANN, E
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: EVALUATION OF SMALL SYNTHETIC PEPTIDES AS CHEMOATTRACTANTS
FOR LEUCOCYTES

OBJECTIVES AND WORK SCOPE : "Evaluation of Small Synthetic Peptides as Chemoattractants for Leucocytes and their Application to Periodontal Disease" is a study which will provide for the synthesis of 20 or more formylmethionyl peptides or related compounds per year. The synthetic procedure will involve well-developed methods with few side reactions. The purification of the compounds should be accomplished with simple recrystallization and ion-exchange methods. The compounds then should be tested for chemotactic activity, effects for increasing molecular size, presence or absence of N-acylation, esterification or amidation of carboxyl groups.

IDENTIFICATION NUMBER..... NO1 DE62497-05
ORGANIZATION..... MAYO FOUNDATION
ADDRESS..... ROCHESTER MINNESOTA
INITIAL START DATE..... 09-30-76
EXPIRATION DATE..... 09-29-81
ORGANIZATION CODE..... 4976101
PROJECT DIRECTOR..... DYCK, PETER J
NIDR PROJECT OFFICER..... DUBNER, RONALD
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: ORAL-FACIAL EVALUATION OF PREVIOUSLY UNTREATED TYPES
OF NEURALGIA

OBJECTIVES AND WORK SCOPE : The Contractor plans to establish whether an abnormality of cutaneous touch-pressure sensation, of pallesthesia, of thermal discrimination and of nociception can (or cannot) be demonstrated in trigeminal neuralgia and in atypical facial neuralgia; compare the type of abnormality of sensation that is found in trigeminal neuralgia and in atypical facial neuralgia; determine whether morphometric and pathologic methods, of Cr V nerve twigs and ganglion, morphologic abnormality can be demonstrated in trigeminal neuralgia.

IDENTIFICATION NUMBER..... NO1 DE72400-04
ORGANIZATION..... BAYLOR COLLEGE OF MEDICINE
ADDRESS..... HOUSTON TEXAS
INITIAL START DATE..... 09-01-77
EXPIRATION DATE..... 08-31-81
ORGANIZATION CODE..... 0481201
PROJECT DIRECTOR..... PEAVY, DUANE L
NIDR PROJECT OFFICER..... FRAZIER, PAUL D
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: IMMUNOPATHOGENESIS OF RECURRENT APHTHOUS STOMATITIS &
BEHCET'S SYNDROME

OBJECTIVES AND WORK SCOPE : This project is a study into the immunopathogenesis of Recurrent Aphthous Stomatitis and Behcet's Syndrome, which will include: measurement of in vitro immune responsiveness of RAS and BS lymphocytes to oral mucosal antigens; determination of tissue specificity of lymphocyte-epithelial cell interactions; investigation of possible bacterial causes of BAS, particularly Streptococcus sanguis; and determination as to whether lymphocytes of RAS and BS patients are thymus-derived (T) or bone marrow-derived (B). The objectives are: to extend and attempt to confirm previous studies as well as to include Behcet's disease, and to determine whether or not a significant correlation exists between the immunological events observed during each exacerbation and whether or not the degree of reactivity correlates with the severity of the disease.

IDENTIFICATION NUMBER..... NO1 DE72404-05
ORGANIZATION..... FLORIDA, UNIVERSITY OF
ADDRESS..... GAINESVILLE FLORIDA
INITIAL START DATE..... 08-15-77
EXPIRATION DATE..... 03-31-81
ORGANIZATION CODE..... 0513806
PROJECT DIRECTOR..... LOTZKAR, S
NIDR PROJECT OFFICER..... SWANGO, PHILIP A
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: EFFECT OF CONCENTRATION & FREQUENCY OF FLUORIDE MOUTHRINSE
ON CARIES

OBJECTIVES AND WORK SCOPE : Test the effectiveness in reducing new caries increment over a three year period of: a 0.5% sodium fluoride mouthrinse (0.0225% F) used daily in school; a 0.2% sodium fluoride (0.09% F) mouthrinse used daily in school; a 0.5% sodium fluoride mouthrinse used weekly in school; and a 0.2% sodium fluoride mouthrinse used weekly in school. To compare the effectiveness of the different concentrations and frequencies.

IDENTIFICATION NUMBER..... NO1 DE72405-08
ORGANIZATION..... LITTON BIONETICS
ADDRESS..... KENSINGTON MARYLAND
INITIAL START DATE..... 08-01-77
EXPIRATION DATE..... 08-31-81
ORGANIZATION CODE..... 0686503
PROJECT DIRECTOR..... GARD, ELIZABETH A
NIDR PROJECT OFFICER..... HOOKS, JOHN
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: ATTEMPT TO INDUCE SJOGREN'S SYNDROME, RECURRENT APHTHOUS
ULCERS & BEHCET'S SYNDROME IN PRIMATES

OBJECTIVES AND WORK SCOPE : Litton Bionetics will provide testing for antinuclear antibody by fluorescent antibody and radioimmunodiffusion assays. Ten rhesus monkeys negative to both tests for antibody will be chosen, all of which are negative to a tuberculin skin test using Old Tuberculin. These animals will be inoculated intracerebrally, intraperitoneally, intravenously, and subcutaneously as directed by the Project Officer with preparations of appropriate biopsy specimens supplied by NIDR. These animals will be maintained for two years and observed daily for early signs of clinical disease. If an animal should develop any disease, NIDR will be notified immediately. A copy of the clinical records of each animal for each four-month period will be supplied to NIDR.

IDENTIFICATION NUMBER..... NO1 DE72407-07
ORGANIZATION..... EASTMAN DENTAL CENTER
ADDRESS..... ROCHESTER NEW YORK
INITIAL START DATE..... 09-30-77
EXPIRATION DATE..... 07-31-81
ORGANIZATION CODE..... 2300901
PROJECT DIRECTOR..... LEVERETT, DENNIS H
NIDR PROJECT OFFICER..... SWANGO, PHILIP A
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: EVALUATION OF TOOTH-CLEANING PRIOR TO RINSING WITH
FLUORIDE SOLUTION

OBJECTIVES AND WORK SCOPE : This project is for a longitudinal clinical research study in which the effect upon dental caries of weekly mouthrinsing with a 0.2% sodium fluoride solution without prior cleaning of the teeth will be compared with the effect of rinsing preceded by cleaning of the teeth, either with a toothbrush alone or with a toothbrush and dental floss.

IDENTIFICATION NUMBER..... NO1 DE72408-06
ORGANIZATION..... STATE UNIV. OF NEW YORK, BUFFALO
ADDRESS..... ALBANY NEW YORK
INITIAL START DATE..... 09-01-77
EXPIRATION DATE..... 08-31-82
ORGANIZATION CODE..... 5992614
PROJECT DIRECTOR..... STINSON, MURRAY W
NIDR PROJECT OFFICER..... KLEIN, DAVID L
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: SEARCH FOR CROSS-REACTION ANTIGENS TO ACIDOGENIC BACTERIA

OBJECTIVES AND WORK SCOPE : A study to search for antigens from nonpathogenic bacteria which cross-react with human oral strains of acidogenic streptococci, lactobacilli, and Actinomyces. Such antigens, if found, might afford more suitable alternative components of anticaries vaccines than cariogenic and acidogenic bacteria and their products.

IDENTIFICATION NUMBER..... NO1 DE72409-08
ORGANIZATION..... EASTMAN DENTAL CENTER
ADDRESS..... ROCHESTER NEW YORK
INITIAL START DATE..... 09-30-77
EXPIRATION DATE..... 12-31-80
ORGANIZATION CODE..... 2300901
PROJECT DIRECTOR..... CURZON, M
NIDR PROJECT OFFICER..... KINGMAN, ALBERT
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: STRONTIUM, LITHIUM & FLUORINE IN VITRO FORMATION OF PLAQUE
IN RATS

OBJECTIVES AND WORK SCOPE : Determine the in vitro effects of various levels of strontium, lithium, and fluorine, both singly and in combination, on the physicochemical, microbiological, and biochemical parameters which are known or thought to contribute significantly to dental plaque formation and activity: adsorption of salivary proteins to hydroxyapatite; sorption of bacteria to hydroxyapatite; bacterial saccharides; bacterial aggregation; and synthesis and breakdown of extracellular polysaccharides. Also, determine the prenatal, preeruptive, and posteruptive effects of various levels of strontium, lithium, and fluorine on plaque formation and caries development in the rat.

IDENTIFICATION NUMBER..... NO1 DE72411-07
ORGANIZATION..... APPLIED MANAGEMENT SCIENCES
ADDRESS..... SILVER SPRING MARYLAND
INITIAL START DATE..... 09-30-77
EXPIRATION DATE..... 09-29-81
ORGANIZATION CODE..... 9643101
PROJECT DIRECTOR..... SKINNER, DOUGLAS E
NIDR PROJECT OFFICER..... SWANGO, PHILIP A
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: ACIDULATED PHOSPHATE-FLUORIDE USED DAILY AS TABLET OR
SOLUTION

OBJECTIVES AND WORK SCOPE : This project is for a longitudinal clinical trial to determine the effect on dental caries of neutral sodium fluoride (NaF) and acidulated phosphate-fluoride (APF) when each is used as a tablet and as a solution. The study population will comprise approximately 1,625 school children, 12-14 years old, who reside in a community where the drinking water contains less than 0.3 ppm fluoride and the school population is relatively stable.

IDENTIFICATION NUMBER..... NO1 DE72499-07
ORGANIZATION..... STATE UNIV. OF NEW YORK, BUFFALO
ADDRESS..... ALBANY NEW YORK
INITIAL START DATE..... 03-14-77
EXPIRATION DATE..... 01-31-81
ORGANIZATION CODE..... 5992614
PROJECT DIRECTOR..... ALBINO, JUDITH E
NIDR PROJECT OFFICER..... HAUSCH, GEORGE H
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: DEVELOPMENT OF METHODS FOR BEHAVIORAL MEASUREMENTS
RELATED TO MALOCCLUSION

OBJECTIVES AND WORK SCOPE : Develop new and meaningful methods for objective and standardized determination of the impact of malocclusion and its treatment. This first phase is specifically to determine whether it is feasible to develop a behavioral and dental instrument that will measure the impact of malocclusion on the individual. Such an instrument is to be pretested on a population of one hundred families with eighth or ninth graders not undergoing or planning orthodontic treatment and fifty families with children who are planning orthodontic treatment. A revised instrument will then be field-tested on another similar population of 150 families.

IDENTIFICATION NUMBER..... NO1 DE82413-05
ORGANIZATION..... EASTMAN DENTAL CENTER
ADDRESS..... ROCHESTER NEW YORK
INITIAL START DATE..... 09-29-78
EXPIRATION DATE..... 12-31-81
ORGANIZATION CODE..... 2300901
PROJECT DIRECTOR..... POLSON, ALAN M
NIDR PROJECT OFFICER..... NISWANDER, JERRY D
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: LONG-TERM EFFECTS OF ORTHODONTIC TREATMENT

OBJECTIVES AND WORK SCOPE : The Contractor will design and conduct a two year study to evaluate the condition of the teeth, supporting structures (gums and bone), and occlusion (bite) of those who have had orthodontic treatment and to compare them with those who have not had orthodontic treatment. A study population of 100 or more patients who have completed full orthodontic treatment more than 10 years ago will be assembled. A suitable control group will also be obtained. The periodontal and general oral health and functional status of the study and control groups will be evaluated using various clinical examinations and measurements and radiographic techniques.

IDENTIFICATION NUMBER.....	NO1 DE82414-04	
ORGANIZATION.....	MAYO FOUNDATION	
ADDRESS.....	ROCHESTER	MINNESOTA
INITIAL START DATE.....	09-30-78	
EXPIRATION DATE.....	09-29-81	
ORGANIZATION CODE.....	4976101	
PROJECT DIRECTOR.....	ROGERS, ROY S	
NIDR PROJECT OFFICER.....	FRAZIER, PAUL D	
NIDR CONTRACT SPECIALIST.....	BLEVINS, MARION	

TITLE: IMMUNOPATHOGENESIS OF RECURRENT APTHOUS STOMATITIS & BEHCET'S SYNDROME

OBJECTIVES AND WORK SCOPE : This project is a study into the immunopathogenesis of Recurrent Aphthous Stomatitis (RAS) and Behcet's Syndrome (BS) to measure in vitro the immune responsiveness of lymphocytes from RAS and BS patients in relation to the severity and stages of the disease, determine if peripheral blood lymphocytes from RAS and BS patients are responsive to oral epithelial antigens and S. sanguis antigens and determine whether lymphocytes of RAS and BS patients are thymus-derived (T) or bone marrow-derived (B). The objectives of the present solicitation are to extend previous studies and to include Behcet's disease, and to determine whether or not a significant correlation exists between the immunological events observed during each exacerbation and whether or not the degree of reactivity correlates with the severity of the disease.

IDENTIFICATION NUMBER..... NO1 DE82415-04
 ORGANIZATION..... CALIFORNIA, UNIVERSITY OF, SAN FRAN
 ADDRESS..... SAN FRANCISCO CALIFORNIA
 INITIAL START DATE..... 09-30-78
 EXPIRATION DATE..... 09-29-81
 ORGANIZATION CODE..... 0577508
 PROJECT DIRECTOR..... GREENSPAN, JOHN S
 NIDR PROJECT OFFICER..... FRAZIER, PAUL D
 NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: IMMUNOPATHOGENESIS OF RECURRENT APTHOUS STOMATITIS &
 BEHCET'S SYNDROME

OBJECTIVES AND WORK SCOPE : Study the immunopathogenesis of Recurrent Aphthous Stomatitis (RAS) and Behcet's Syndrome (BS) to: measure in vitro the immune responsiveness of lymphocytes from RAS and BS patients in relation to the severity and stages of the disease; determine if peripheral blood lymphocytes from RAS and BS patients are responsive to oral epithelial antigens and S. sanguis antigens; and determine whether lymphocytes of RAS and BS patients are thymus-derived (T) or bone marrow-derived (B). The present objectives are to: extend previous studies and include Behcet's disease; and determine whether or not a significant correlation exists between the immunological events observed during each exacerbation and whether or not the degree of reactivity correlates with the severity of the disease.

IDENTIFICATION NUMBER..... NO1 DE82416-02
ORGANIZATION..... TEXAS HEALTH SCI. CENTER, UNIVERSITY
ADDRESS..... HOUSTON TEXAS
INITIAL START DATE..... 09-30-78
EXPIRATION DATE..... 01-28-82
ORGANIZATION CODE..... 0578417
PROJECT DIRECTOR..... FRIEDMAN, LAWRENCE A
NIDR PROJECT OFFICER..... SWANGO, PHILIP A
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: EFFECT OF DAILY MOUTHRINSING WITH STANNOUS FLUORIDE
OR SODIUM FLUORIDE

OBJECTIVES AND WORK SCOPE : The Contractor will implement a 3-year longitudinal clinical trial to study the effects of mouthrinsing with stannous fluoride and sodium fluoride upon the development of dental caries, dental plaque, gingivitis, and extrinsic tooth staining. A test population of approximately 500 students will be utilized, one half of the subjects rinsing once a day in school with 10 ml. of a 0.1% solution of stannous fluoride (SnF₂) and the other half rinsing once a day in school with 10 ml. of a 0.05% solution of sodium fluoride (NaF).

IDENTIFICATION NUMBER..... NO1 DE82417-04
ORGANIZATION..... EASTMAN DENTAL CENTER
ADDRESS..... ROCHESTER NEW YORK
INITIAL START DATE..... 09-30-78
EXPIRATION DATE..... 09-29-81
ORGANIZATION CODE..... 2300901
PROJECT DIRECTOR..... LEVERETT, DENNIS H
NIDR PROJECT OFFICER..... SWANGO, PHILIP A
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: EFFECT OF DAILY MOUTHRINSING WITH STANNOUS FLUORIDE
OR SODIUM FLUORIDE

OBJECTIVES AND WORK SCOPE : The Contractor will implement a 3-year longitudinal clinical trial to study the effects of mouthrinsing with stannous fluoride and sodium fluoride upon the development of dental caries, dental plaque, gingivitis, and extrinsic tooth staining. A test population of approximately 500 students will be utilized, one half of the subjects rinsing once a day in school with 10 ml. of a 0.1% solution of stannous fluoride (SnF₂) and the other half rinsing once a day in school with 10 ml. of a 0.05% solution of sodium fluoride (NaF).

IDENTIFICATION NUMBER..... NO1 DE92418-05
ORGANIZATION..... AMERICAN TYPE CULTURE COLLECTION
ADDRESS..... ROCKVILLE MARYLAND
INITIAL START DATE..... 12-01-78
EXPIRATION DATE..... 03-31-82
ORGANIZATION CODE..... 0397101
PROJECT DIRECTOR..... GHERNA, ROBERT L
NIDR PROJECT OFFICER..... KRICHEVSKY, MICAH I
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: CHARACTERIZATION & IDENTIFICATION OF PLEOMORPHIC ORAL BACTERIA

OBJECTIVES AND WORK SCOPE : The Contractor will establish a set of well authenticated strains of various genera of oral microorganisms which will be available for distribution to oral microbiologists; compare results of various common media and methods for assessing the same properties; build a data base describing both authenticated laboratory strains and fresh clinical isolates; and construct and test a probability system for identification of pleomorphic bacteria from the oral cavity.

IDENTIFICATION NUMBER..... NO1 DE92419-03
ORGANIZATION..... STATE UNIV. OF NEW YORK, STONY BRO
ADDRESS..... ALBANY NEW YORK
INITIAL START DATE..... 01-15-79
EXPIRATION DATE..... 01-14-82
ORGANIZATION CODE..... 5992612
PROJECT DIRECTOR..... RIPA, LOUIS W
NIDR PROJECT OFFICER..... SWANGO, PHILIP A
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: EFFECT OF PRIOR TOOTHCLEANING ON EFFICACY OF SEMIANNUAL
FLUORIDE TREATMENT

OBJECTIVES AND WORK SCOPE : This procurement is for the conduct of a longitudinal study to assess the effect of prior toothcleaning upon the anticaries efficacy of semiannual professionally applied topical fluoride treatments. The proposed study will provide a comparison of the efficacy of semiannual professionally administered APF gel treatments when preceded by either a conventional pumice prophylaxis, self-cleaning of the teeth by subjects using a toothbrush and dental floss, or no tooth cleaning.

Three study groups will be established, each containing approximately one-third of the subjects at the beginning of the study. Subjects will be randomly assigned to groups. Subjects in Group I will receive semiannually a professional application of acidulated phosphate-fluoride gel that contains 1.23% fluoride and has a pH of approximately 3.0. Each gel application will be preceded by a thorough dental prophylaxis. Calculus will be removed as necessary. Group II will receive semiannual fluoride gel applications as described for Group I, except that prior to gel applications subjects will thoroughly clean their own teeth with a toothbrush, dentifrice, and dental floss. A professional prophylaxis will not be administered. Subjects in Group III will receive semiannual fluoride gel treatments as described for Groups I and II, except that no toothcleaning of any kind will be performed prior to treatment.

IDENTIFICATION NUMBER..... NO1 DE92420-07
ORGANIZATION..... MICROBIOLOGICAL ASSOCIATES
ADDRESS..... BETHESDA MARYLAND
INITIAL START DATE..... 05-01-79
EXPIRATION DATE..... 11-18-81
ORGANIZATION CODE..... 5251602
PROJECT DIRECTOR..... DINOWITZ, MARSHALL
NIDR PROJECT OFFICER..... MCCLINTOCK, PATRICK
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: SEARCH FOR DIABETOGENIC VIRUSES

OBJECTIVES AND WORK SCOPE : Provide services for a two-part screening procedure for detecting diabetogenic viruses. An estimated forty candidate diabetogenic viruses (provided by the Government) will be screened for their capacity to alter glucose homeostasis by infecting pancreatic islet cells of mice and rats. Results will be tabulated on data sheets and provided to the Government.

IDENTIFICATION NUMBER.....	NO1 DE92421-14	
ORGANIZATION.....	WESTAT, INC.	
ADDRESS.....	ROCKVILLE	MARYLAND
INITIAL START DATE.....	04-15-79	
EXPIRATION DATE.....	01-31-81	
ORGANIZATION CODE.....	9611701	
PROJECT DIRECTOR.....	MCKENNA, THOMAS W	
NIDR PROJECT OFFICER.....	MILLER, ANN	
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH	

TITLE: SURVEY OF DENTAL CARIES PREVALENCE IN SCHOOL CHILDREN
THROUGHOUT THE US

OBJECTIVES AND WORK SCOPE : Plan and conduct the gathering of data for a survey of the prevalence of dental caries among school aged children in the continental United States. Develop and utilize a probability sample according to NIDR specifications of children in grades Kindergarten through twelve (K-12). Conduct examinations for dental caries, gingivitis, and need for dental treatment on children in randomly selected classrooms; record their residence history; obtain and record the fluoride content of their drinking water; and provide these data to the NIDR. Examinations will be conducted during the 1979-1980 school year.

IDENTIFICATION NUMBER..... NO1 DE92422-04
ORGANIZATION..... COLUMBIA UNIVERSITY
ADDRESS..... NEW YORK NEW YORK
INITIAL START DATE..... 09-27-79
EXPIRATION DATE..... 09-26-82
ORGANIZATION CODE..... 1742301
PROJECT DIRECTOR..... ELLISON, SOLON A
NIDR PROJECT OFFICER..... KLEIN, DAVID L
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: DENTAL PLAQUE AND SALIVA FROM GASTRIC-INTUBATED PATIENTS

OBJECTIVES AND WORK SCOPE : Investigate a minimum of 25 gastric-intubated patients to perform detailed analysis of the microbiological, immunological, and biochemical constituents in dental plaque and saliva. Control subjects will be an equivalent number of age-matched volunteers who are staff, students, or patients at the Columbia-Presbyterian Medical Center. Samples will be taken from plaque which will be allowed to develop for four days after prophylaxis. Saliva samples will be collected after the initial cleaning prior to plaque accumulation.

IDENTIFICATION NUMBER..... NO1 DE92423-01
ORGANIZATION..... MINNESOTA, UNIVERSITY OF
ADDRESS..... ST. PAUL MINNESOTA
INITIAL START DATE..... 09-29-79
EXPIRATION DATE..... 09-28-81
ORGANIZATION CODE..... 5365601
PROJECT DIRECTOR..... SINGER, LEON
NIDR PROJECT OFFICER..... FRAZIER, PAUL D
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: MAINTENANCE OF A SPECIAL MOUSE COLONY FOR FLUORIDE RESEARCH

OBJECTIVES AND WORK SCOPE : Maintain a special mouse colony for fluoride research for the purpose of providing animals to qualified investigators. The animals will live on a defined fluoride intake (high and low levels) for at least five years, or approximately ten generations.

IDENTIFICATION NUMBER..... YO1 DE00001-02
ORGANIZATION..... VETERANS ADMINISTRATION HOSPITAL
ADDRESS..... EAST ORGANGE NEW JERSEY
INITIAL START DATE..... 04-01-80
EXPIRATION DATE..... 06-30-82
ORGANIZATION CODE..... 0481053
PROJECT DIRECTOR..... MASHBERG, ARTHUR
NIDR PROJECT OFFICER..... GOGGINS, JOHN F
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: RELATIONSHIP OF ALCOHOL CONSUMPTION TO DEVELOPMENT OF
ORAL CANCER

OBJECTIVES AND WORK SCOPE : The VA hospital will conduct the
necessary activities to identify potential populations for
studies of the relationship of alcohol consumption to the
development of oral cancer.

IDENTIFICATION NUMBER..... YO1 DE10001-00
ORGANIZATION..... U.S. DEPARTMENT OF HLTH & HUMAN SERVICE
ADDRESS..... SAN FRANCISCO CALIFORNIA
INITIAL START DATE..... 10-14-80
EXPIRATION DATE..... 04-15-81
ORGANIZATION CODE..... 0485454
PROJECT DIRECTOR..... WEINSTEIN, SHERIDAN
NIDR PROJECT OFFICER..... FREW, RALPH A
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: SEALANT TOPICAL FLUORIDE PROGRAM IN CALIFORNIA USING
DENTAL ASSISTANTS

OBJECTIVES AND WORK SCOPE : A study of the feasibility of
conducting a study of the cost and effectiveness of training
and utilizing dental assistants for the delivery of caries
prevention agents and techniques in a school-based program.

IDENTIFICATION NUMBER..... YO1 DE10003-00
ORGANIZATION..... VETERANS ADMINISTRATION HOSPITAL
ADDRESS..... SEPULVEDA CALIFORNIA
INITIAL START DATE..... 10-01-80
EXPIRATION DATE..... 09-30-81
ORGANIZATION CODE..... 0481017
PROJECT DIRECTOR..... KAPUR, KRISHAN K.
NIDR PROJECT OFFICER..... CHRISTIANSEN, R L
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: CRANIOFACIAL NORMS IN ADULTS

OBJECTIVES AND WORK SCOPE : The project will attempt to establish normative data for craniofacial dimensions of hard and soft tissue in adults, from the third to the eighth decade of life. The study will be cross-sectional in nature and will be conducted on records obtained from a sizeable sample of VA patients. The ultimate aim of this project is to develop a computerized system for the fabrication of dentures and to define clinical standards that can be applied in assessing the dental needs of partially or totally edentulous patients.

IDENTIFICATION NUMBER..... YO1 DE10004-00
ORGANIZATION..... U.S. PHS HOSPITAL
ADDRESS..... SAN FRANCISCO CALIFORNIA
INITIAL START DATE..... 10-01-80
EXPIRATION DATE..... 10-30-83
ORGANIZATION CODE..... 0485411
PROJECT DIRECTOR..... MOFFA, JOSEPH P
NIDR PROJECT OFFICER..... MOFFA, JOSEPH P
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: CLINICAL EVALUATION OF DENTAL RESTORATIVE MATERIALS .

OBJECTIVES AND WORK SCOPE :

1. Evaluate Base-Metal Alloys and Ceramic Materials.
 - a. Determine the relationship between nickel sensitivity and the presence of intraoral nickel containing fixed prosthodontic dental alloys.
 - b. Investigate in vitro ceramic and dental casting alloys.
2. Evaluate Composite Resins.

Continue the long-term assessment of the clinical performance of composite resins for the restoration of posterior teeth and quantify the occlusal wear of composite resins.
3. Evaluate Amalgam Alloys.

Continue the long-term assessment of the clinical performance of amalgam alloy formulations.
4. Improve Computer Technology in Clinical Research and Expand its use to in vitro Biomaterial Research.
5. Compile, analyze, and publish previously obtained data.

IDENTIFICATION NUMBER..... YO1 DE10005-00
ORGANIZATION..... U.S. DEPARTMENT OF AGRICULTURE
ADDRESS..... LOGAN UTAH
INITIAL START DATE..... 02-01-81
EXPIRATION DATE..... 09-30-81
ORGANIZATION CODE..... 8551901
PROJECT DIRECTOR..... KEELER, RICHARD F
NIDR PROJECT OFFICER..... BROWN, KENNETH S
NIDR CONTRACT SPECIALIST..... MULLEN, EDITH

TITLE: STUDY OF TERATOGENIC PLANT ALKALOIDS FROM VERATRUM,
CALIFORNIA

OBJECTIVES AND WORK SCOPE : NIDR has shown, in a collaborative effort with the Poisonous Plant Research Laboratory, USDA, Ogden, Utah, that mice from different genetic lines differ in their response to these alkaloids. In some cases there appears to be a specific interaction between the genotype and the drug as a specific biochemical effect. NIDR wishes to further explore these findings and to explore the nature of the mechanism of the teratogenic effect. NIDR will seek to accomplish this goal by in vivo and in vitro experiments using the isolated alkaloids as well as radioactive forms prepared from those isolated alkaloids. Dr. Keeler of USDA will collaborate with NIDR by collecting fresh plants and purifying the alkaloids to supply the needs of the cooperative study.

IDENTIFICATION NUMBER..... YO1 DE10007-00
ORGANIZATION..... U.S. NATIONAL BUREAU OF STANDARDS
ADDRESS..... WASHINGTON DISTRICT OF COLUMBIA
INITIAL START DATE..... 06-01-81
EXPIRATION DATE..... 09-30-83
ORGANIZATION CODE..... 5644902
PROJECT DIRECTOR..... MOTZ, J. W.
NIDR PROJECT OFFICER..... REESE, JOYCE A
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: DENTAL RADIOGRAPHIC SYSTEM WITH SELECTIVE GEOMETRY .

OBJECTIVES AND WORK SCOPE : The investigators of the project will attempt to design and build an experimental dental radiographic source-detector system having electronically controlled exposure geometry. The detector of the system shall yield a time-varying electronic signal which when interfaced to a cathode ray display controlled by a digital computer will yield a radiographic image. This system should be capable of producing radiographic data amenable to reproducible geometric registration from one examination to the next to facilitate sequential analysis of common dental pathologies (i.e., periodontal disease, caries, etc.).

This system will be specifically designed to interface with an image processing computer to be used for experimental research by the Diagnostic Methodology Section of the NIDR.

IDENTIFICATION NUMBER..... YO1 DE10009-00
ORGANIZATION..... U.S. ARMED FORCES RADIOBIOLOGY RES
ADDRESS..... BETHESDA MARYLAND
INITIAL START DATE..... 07-01-81
EXPIRATION DATE..... 09-30-81
ORGANIZATION CODE..... 2063904
PROJECT DIRECTOR..... SMOKER, RONALD R
NIDR PROJECT OFFICER..... BOWEN, WILLIAM H
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: STUDY TO DETERMINE EFFECT OF SUSTAINED RELEASE FLUORIDE

OBJECTIVES AND WORK SCOPE : AFRRI will irradiate eight monkeys in the head and neck region, using a suitable source of radiation to inactivate the major salivary glands. The animals will receive 250 rads twice a week for two weeks on each side of the head and neck, and once in the third week. This study is part of an investigation to determine the effect of sustained release fluoride on "irradiation" caries in primates.

IDENTIFICATION NUMBER..... YO1 DE40014-08
ORGANIZATION..... VETERANS ADMINISTRATION HOSPITAL
ADDRESS..... EAST ORANGE NEW JERSEY
INITIAL START DATE..... 01-01-74
EXPIRATION DATE..... 09-30-81
ORGANIZATION CODE..... 0481053
PROJECT DIRECTOR..... MASHBERG, ARTHUR
NIDR PROJECT OFFICER..... FRAZIER, PAUL D
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: TECHNIQUES FOR EARLY DETECTION OF ORAL CARCINOMA .

OBJECTIVES AND WORK SCOPE : A study to develop and evaluate clinical criteria for the early detection of oral carcinoma and to evaluate toluidine blue and a DNA-acridine binding test as techniques for identifying patients with precancerous field alterations of the oral mucosa.

IDENTIFICATION NUMBER.....	Y01 DE40015-13
ORGANIZATION.....	U.S. NATIONAL BUREAU OF STANDARDS
ADDRESS.....	WASHINGTON DISTRICT OF COLUMBIA
INITIAL START DATE.....	07-01-73
EXPIRATION DATE.....	09-30-81
ORGANIZATION CODE.....	5644902
PROJECT DIRECTOR.....	CASSEL, JAMES M
NIDR PROJECT OFFICER.....	REESE, JOYCE A
NIDR CONTRACT SPECIALIST.....	MULLEN, EDITH

TITLE: INTERACTIONS OF ORAL STRUCTURES & RESTORATIVE MATERIALS

OBJECTIVES AND WORKSCOPE : The study is being performed to obtain new knowledge on the properties and interactions of oral structures and restorative materials. The subject matter to be explored and studied, including subtasks, is as follows:

1. Adhesion of Restorative and Caries-Preventive Materials to Tooth Surfaces
 - A. Surface Characterization of Dental Materials by Water Adsorption
 - B. Novel Approach to Development and Assessment of Adhesion in Dental Materials
 - C. Synthesis for Improved Adhesion and Stability of Composite Restorative and Sealant Materials
 - D. Polymer Grafting, A Technique for Bonding to Mineralized Collagen Surfaces
2. Physical, Mechanical and Physicochemical Properties of Hard and Soft Tissues of Dental Materials
 - A. Dimensional Changes in Tooth Structure
 - B. Wear-Resistance of Dental Restorative Materials
 - C. Zinc-Polycarboxylate Dental Cement, Properties and Technique for Improvement

IDENTIFICATION NUMBER..... YO1 DE90003-03
ORGANIZATION..... INDIAN HEALTH SERVICE, HSA, DHHS
ADDRESS..... SHIPROCK NEW MEXICO
INITIAL START DATE..... 07-01-79
EXPIRATION DATE..... 09-30-82
ORGANIZATION CODE..... 0485419
PROJECT DIRECTOR..... BECK, C. MICHAEL
NIDR PROJECT OFFICER..... NISWANDER, JERRY D
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: LONG-TERM EVALUATION OF SERIAL EXTRACTION IN NAVAJO CHILDREN

OBJECTIVES AND WORK SCOPE : This 3-month agreement is for Phase I of a bi-phasic 18-month effort to assess the long-term results of serial extraction carried out in a Navajo population 10-12 years ago. Phase I is limited to the inventory and catalog of existing records and determination of subject availability. Based upon a review of the completeness of existing records and availability of subjects, the conduct of Phase II will be considered.

IDENTIFICATION NUMBER..... NO1 AI52530-07
ORGANIZATION..... BETH ISRAEL HOSPITAL
ADDRESS..... BOSTON MASSACHUSETTS
INITIAL START DATE..... 06-30-75
EXPIRATION DATE..... 06-30-81
ORGANIZATION CODE..... 0758101
PROJECT DIRECTOR..... FREEDBERG, IRWIN M
NIDR PROJECT OFFICER..... FRAZIER, PAUL D
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: THERAPY OF CUTANEOUS HERPES SIMPLEX IN NORMAL & COMPRISED
HOSTS

OBJECTIVES AND WORK SCOPE : The Contractor will conduct studies to better define the natural history of facial mucocutaneous herpesvirus hominis infections and to determine the safety and estimate the efficacy of monophosphate adenine arabinoside and disodium phosphonoacetate when used topically in the treatment of confirmed facial mucocutaneous herpesvirus hominis infections.

IDENTIFICATION NUMBER..... NO1 AI52532-07
ORGANIZATION..... UTAH, UNIVERSITY OF
ADDRESS..... SALT LAKE CITY UTAH
INITIAL START DATE..... 06-30-75
EXPIRATION DATE..... 06-30-81
ORGANIZATION CODE..... 0514002
PROJECT DIRECTOR..... OVERALL, JAMES C
NIDR PROJECT OFFICER..... FRAZIER, PAUL D
NIDR CONTRACT SPECIALIST..... BLEVINS, MARION

TITLE: STUDY OF RECURRENT MUCOCUTANEOUS HERPESVIRUS HOMINIS
INFECTION

OBJECTIVES AND WORK SCOPE : The Contractor will conduct studies to better define the natural history of facial mucocutaneous herpesvirus hominis infections and to determine the safety and estimate the efficacy of monophosphate adenine arabinoside and disodium phosphonoacetate when used topically in the treatment of confirmed facial mucocutaneous herpesvirus hominis infections.

PART VI

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

INDEXES

October 1, 1980 - September 30, 1981

This document was prepared for administrative use at NIH. The comments and declarations of its contributors are their own and do not necessarily represent an official statement of the Institute.

Compiled By

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

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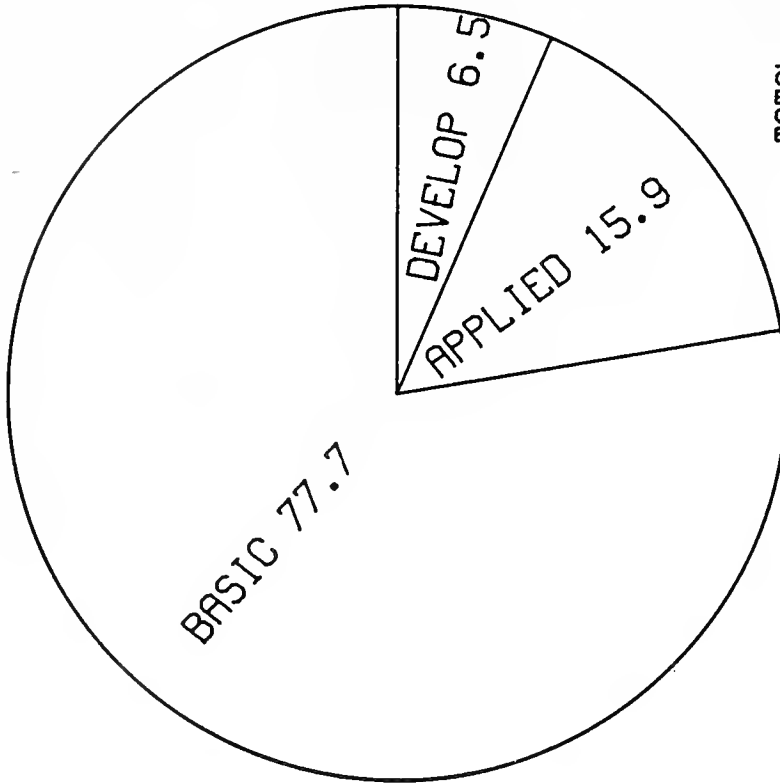
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B A D

S A T T



TOTAL - \$12,003,563

*NOTE: B A D - BASIC, APPLIED & DEVELOPMENT
S A T T - SCIENCE BASED, APPLIED, TRANSFER & TRAINING
TRANSFER & TRAINING LESS THAN 1%

 ** DISTRIBUTION OF NIDR INTRAMURAL **
 ** RESEARCH DESIGNATIONS FY 1981 **
 **
 ** TOTAL OBLIGATED: \$12,003,563 **

	B A S I C	A P P L I E D	D E V E L O P M E N T	T O T A L N I D R
INTRAMURAL	9,212,013 83.0	1,340,950 12.1	539,505 4.9	\$11,092,468
NCP	113,201 12.4	562,814 61.8	235,080 25.8	911,095
TOTAL NIDR	9,325,214 77.7	1,903,764 15.9	774,585 6.4	\$12,003,563

	S C I E N C E B A S E D	A P P L I E D	T R A N S F E R	T O T A L N I D R
INTRAMURAL	10,552,958 95.1	539,505 4.9	0 .0	\$11,092,463
NCP	676,020 74.2	200,128 22.0	34,952 3.8	911,100
TOTAL NIDR	11,228,978 93.5	739,633 6.2	34,952 .3	\$12,003,563

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R01DE-01374-21 (PBC) VEIS, ARTHUR, NORTHWESTERN UNIVERSITY, 303 EAST CHICAGO AVENUE, CHICAGO, ILL 60611 Matrix component interactions in calcified tissues (cattle, rats, chickens, h).

R01DE-01554-20 (OBM) MANDEL, IRWIN D, COLUMBIA UNIVERSITY, 630 WEST 168TH STREET, NEW YORK, N Y 10032 Host factors in caries resistance (human, rats).

P01DE-01697-19 (SSS) FORREST, EDWARD J, 3501 TERRACE STREET, PITTSBURGH, PA 15261.

P01DE-01697-19 0035 (SSS) DOYLE, WILLIAM J. --Non-human primate model of cleft palate (monkeys).

P01DE-01697-19 0036 (SSS) FISHER, STANLEY E. --Evaluation of velopharyngeal sphincter function (human).

P01DE-01697-19 0037 (SSS) GLASER, ELLEN R. --Effects of oronasal fistulae on speech (human).

P01DE-01697-19 0038 (SSS) LANGDON, HERBERT L. --Anatomy of the posterior pharyngeal wall.

P01DE-01697-19 0039 (SSS) PARADISE, JACK L. --Otitis media and its consequences (human).

P01DE-01697-19 0040 (SSS) SIEGEL, MICHAEL I. --Pattern recognition for reconstruction of nasal capsular anatomy.

P01DE-01697-19 0041 (SSS) STOOL, SYLVAN E. --Effect of palate repair on eustachian tube function (human).

R01DE-01830-19 (OBM) HIGUCHI, WILLIAM I, UNIVERSITY OF MICHIGAN, COLLEGE OF PHARMACY, ANN ARBOR, MICH 48109 Quantitation of enamel demineralization mechanisms.

P01DE-01850-18 (SSS) SINGER, LEON, UNIVERSITY OF MINNESOTA, 227 MILLARD HALL, MINNEAPOLIS, MINN 55455 Nutritional sources and metabolic roles of fluoride.

P01DE-01850-18 0068 (SSS) SINGER, LEON. Nutritional sources and metabolic roles of fluoride--Radioimmunoassay of parathyroid hormone in the rat.

P01DE-01850-18 0071 (SSS) SINGER, LEON. Nutritional sources and metabolic roles of fluoride--Fluoride content of infant, toddler and adult foods.

P01DE-01850-18 0072 (SSS) CARR, C W. Nutritional sources and metabolic roles of fluoride--Effect of fluoride on iron transport (mice).

P01DE-01850-18 0075 (SSS) OPHAUG, ROBERT H. Nutritional sources and metabolic roles of fluoride--Metabolic handling of perfluorooctanoic acid (rats).

P01DE-01850-18 0081 (SSS) SINGER, LEON. Nutritional sources and metabolic roles of fluoride--Effect of fluoride intake on strain N mice.

P01DE-01850-18 0082 (SSS) SINGER, LEON. Nutritional sources and metabolic roles of fluoride--Nonionic fluoride in foods (human).

P01DE-01850-18 0084 (SSS) SINGER, LEON. Nutritional sources and metabolic roles of fluoride--Enamel, dentin and cementum in osteogenesis imperfecta (human).

P01DE-01850-18 0085 (SSS) SINGER, LEON. Nutritional sources and metabolic roles of fluoride--Absorption of fluoride from dietary substances (rats).

P01DE-01850-18 0086 (SSS) SINGER, LEON. Nutritional sources and metabolic roles of fluoride--Effect of fluoride intake on serum alkaline phosphatase activity (mice).

P01DE-01850-18 0087 (SSS) OPHAUG, ROBERT H. Nutritional sources and metabolic roles of fluoride--Methodology for determining ionic fluoride content of human plasma.

P01DE-01850-18 0088 (SSS) SINGER, LEON. Nutritional sources and metabolic roles of fluoride--Fluoride and glycosaminoglycans in bone (mice).

P01DE-01850-18 0089 (SSS) OPHAUG, ROBERT H. Nutritional sources and metabolic roles of fluoride--Effect of skeletal fluoride load on retention of administered fluoride.

R01DE-01912-18 (OBM) YOUNG, ROBERT A, GEORGIA INST OF TECHNOLOGY, ENGINEERING EXPERIMENT STATION, ATLANTA, GA 30332 Tooth enamel apatite at the atomic level (human).

R01DE-02103-17 (SSS) URIST, MARSHALL R, UNIVERSITY OF CALIFORNIA, 1000 VETERAN AVENUE, LOS ANGELES, CALIF 90024 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human).

R01DE-02110-17 (PHY) SCHNEYER, CHARLOTTE A, UNIVERSITY OF ALA, UNIVERSITY STATION, BIRMINGHAM, ALA 35294 Salivary gland structure and function (rats).

R01DE-02212-13 (OBM) MEYER, MAURICE W, UNIVERSITY OF MINNESOTA, 424 MILLARD HALL, MINNEAPOLIS, MINN 55455 Circulation in teeth and supporting structures (dogs, monkeys).

R01DE-02320-16 (OBM) MAHLER, DAVID B, UNIVERSITY OF OREGON HLTH CENT, PORTLAND, OREG 97201 Clinical behavior of dental restorative materials.

N01DE-02427-04 (**) WHISTLER, ROY L, WEST LAFAYETTE, INDIANA Synthesize noncarcinogenic sweeteners.

N01DE-02428-04 (**) COOK, CLARENCE E, RESEARCH TRIANGLE PARK, NORTH CAROLINA Synthesis of noncarcinogenic sweeteners (mice).

R01DE-02525-16 (OBM) SIMMELINK, JAMES W, CASE WESTERN RESERVE UNIV, 2123 ABINTON ROAD, CLEVELAND, OHIO 44106 Ultrastructural histopathology of human dental enamel.

P50DE-02600-15 (DSR) PAGE, ROY C, UNIVERSITY OF WASHINGTON, CENTER/RESEARCH IN ORAL BIOL., SEATTLE, WASH 98195.

P50DE-02600-15 0003 (DSR) BORNSTEIN, PAUL A. --Disorders of connective tissue metabolism (human).

P50DE-02600-15 0014 (DSR) CLAGETT, JAMES A. --Periodontal diseases (human, rats).

P50DE-02600-15 0023 (DSR) STORR, URSULA B. --Regulation of antibody response (mice, rabbits).

P50DE-02600-15 0028 (DSR) BAYLINK, DAVID J. --Repletion and coupling in bone volume regulation (rat).

P50DE-02600-15 0030 (DSR) ALTMAN, LEONARD C. --Leukocyte function--Its role in periodontal disease (human).

P50DE-02600-15 0032 (DSR) DALE, BEVERLY A. --Keratinohyalin in keratinization of oral mucosa and skin (human, rats).

P50DE-02600-15 0034 (DSR) IZUTSU, KENNETH T. --Salivary and oral mucosal changes after cancer chemotherapy.

P50DE-02600-15 0035 (DSR) KENNY, GEORGE E. --Serotyping of microbes for diagnosis of periodontitis (rabbits).

P50DE-02600-15 0037 (DSR) WILLIAMS, BETSY L. --Periodontal microflora (human).

P50DE-02600-15 0039 (DSR) FRETWELL, MARSHA D. --Saliva in abnormal bacterial adherence and colonization (human).

P50DE-02600-15 0040 (DSR) BIRDSELL, D C. --Fate of actinomyces viscosus components within phagocytic cells.

P50DE-02600-15 0041 (DSR) PAGE, ROY C. --Perio treatment (human).

P50DE-02600-15 9001 (DSR) PAGE, ROY C. --Core.

P50DE-02623-14 (DSR) ROSENBLUM, JOEL, UNIVERSITY OF PENNSYLVANIA, 4001 SPRUCE STREET, PHILADELPHIA, PA 19104 Center for oral health research.

P50DE-02623-14 0002 (DSR) COHEN, GARY H. Center for oral health research--Major structural proteins of herpes simplex virus.

P50DE-02623-14 0005 (DSR) HAMMOND, BENJAMIN F. Center for oral health research--Mechanisms of pathogenicity in two groups of periodontopathic bacteria.

P50DE-02623-14 0009 (DSR) LISTGARTEN, MAX A. Center for oral health research--Oral microorganisms in periodontal health and disease (human, rats).

P50DE-02623-14 0013 (DSR) MONTGOMERY, PAUL C. Center for oral health research--Mechanisms of secretory antibody induction.

P50DE-02623-14 0014 (DSR) ROSAN, BURTON. Center for oral health research--Surface receptors on plaque forming organisms.

P50DE-02623-14 0023 (DSR) MCARTHUR, WILLIAM P. Center for oral health research--Interactions of oral bacteria and polymorphonuclear leukocytes.

P50DE-02623-14 0026 (DSR) ROSENBLUM, JOEL. Center for oral health research--Collagen biosynthesis in the periodontium.

P50DE-02623-14 0027 (DSR) CHRISTNER, PAUL. Center for oral health research--Collagenase in the periodontium.

P50DE-02623-14 0030 (DSR) SHAPIRO, IRVING M. Center for oral health research--Role of mitochondria in the mineralization process (chickens).

P50DE-02623-14 0031 (DSR) NOWOTNY, ALOIS H. Center for oral health research--Role of immunity in periodontal disease (rats).

P50DE-02623-14 0032 (DSR) MALAMUD, D. Center for oral health research--Interactions of salivary agglutinins and oral bacteria.

P50DE-02623-14 0033 (DSR) PLISKIN, MICHAEL E. Center for oral health research--Immune system in regulation of angiogenesis.

P50DE-02668-15 (DSR) HIRSCH, PHILIP F, UNIVERSITY OF NORTH CAROLINA, DENTAL RESEARCH CENTER, CHAPEL HILL, N C 27514.

P50DE-02668-15 0088 (DSR) TOVERUD, S U. --Hypervitaminosis D in lactation.

P50DE-02668-15 0123 (DSR) KUSY, ROBERT P. --In situ replication techniques and the wear of restorative materials.

P50DE-02668-15 0125 (DSR) MECHANIC, GERALD L. --Collagen crosslinks and the fate of extracellular matrix.

P50DE-02668-15 0149 (DSR) TURNER, DEREK T. --Strengths of polymers in tooth restorative materials.

P50DE-02668-15 0150 (DSR) TURNER, DEREK T. --Polymerization of tooth restorative composite materials.

P50DE-02668-15 0151 (DSR) BAWDEN, JAMES W. --Factors controlling the flux of ions into developing enamel.

P50DE-02668-15 0152 (DSR) LUNDBLAD, ROGER L. --Primary structure of proteins in hemostasis and oral biology.

P50DE-02668-15 0168 (DSR) WHITE, GILBERT C. --Thrombin-platelet interactions (human).

P50DE-02668-15 0172 (DSR) JOHNSTON, MALCOLM C. --Genetic and environmental factors interaction in development of cleft lip (mice).

P50DE-02668-15 0176 (DSR) MECHANIC, GERALD L. --Collagen biochemistry and the myeloblastosis associated virus infected cells.

P50DE-02668-15 0190 (DSR) LUNDBLAD, ROGER L. --Thrombin and prothrombin.

P50DE-02668-15 0191 (DSR) LEINFELDER, KARL F. --Clinical evaluation of restorative materials and techniques.

P50DE-02668-15 0192 (DSR) HIRSH, PHILIP F. --Skeletal actions of calcitonin in the rat.

P50DE-02668-15 0193 (DSR) CRENSHAW, M A. --Metabolism of isolated ameloblasts.

P50DE-02668-15 0196 (DSR) HANKER, JACOB S. --Cytochemical demonstration of macromolecules of craniofacial tissue.

P50DE-02668-15 0197 (DSR) HANKER, JACOB S. --Peripheral nerves of the orofacial region.

P50DE-02668-15 0199 (DSR) WHITSEL, BARRY L. --Mechanisms governing the behavior of somatosensory cerebral cortical neurons.

P50DE-02668-15 0200 (DSR) WHITSEL, BARRY L. --Response of first order mechanoreceptive afferents to moving tactile stimuli.

P50DE-02668-15 0204 (DSR) DREYER, DUANE A. --Psychophysical measures of combined tactile and thermal sensitivity (human).

P50DE-02668-15 0207 (DSR) BAWDEN, JAMES W. --Effects of vitamin A and D, PTH, CT on uptake of calcium and phosphorus in enamel.

P50DE-02668-15 0208 (DSR) DREYER, DUANE A. --Effects of skin warming on neural responses to tactile stimuli.

P50DE-02668-15 0209 (DSR) DREYER, DUANE A. --Static and dynamic properties of S-I neurons in the behaving macaque monkey.

P50DE-02668-15 0210 (DSR) WHITSEL, BARRY L. --Somesthetic capacities of human subjects (monkeys).

P50DE-02668-15 0211 (DSR) HANKER, JACOB S. --Salivary glands and their innervation in diabetes (mice).

** SEE GLOSSARY OF ABBREVIATIONS for explanation of grant and contract number

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- P50DE-02668-15 0212 (DSR) SULIK, KATHLEEN M. --Determination of risk related to alcohol consumption before pregnancy recognition.
- P50DE-02668-15 0213 (DSR) COFFEY, JAMES C. --Hormone action is the salivary glands of inbred mice.
- P50DE-02668-15 0214 (DSR) WARREN, DONALD W. --Motor control during speech.
- P50DE-02670-15 (DSR) FULLMER, HAROLD M, UNIVERSITY OF ALABAMA, UNIVERSITY STATION, BIRMINGHAM, ALA 35294.
- P50DE-02670-15 0001 (DSR) BUGG, CHARLES E. --Crystal structures of calcium and phosphate complexes and of related proteins.
- P50DE-02670-15 0003 (DSR) BUTLER, WILLIAM T. --Biochemistry of collagenous and noncollagenous proteins of connective tissues.
- P50DE-02670-15 0014 (DSR) KOULOURIDES, THEODORE. --Mechanism of production of carious lesions.
- P50DE-02670-15 0018 (DSR) MESTECKY, JIRI F. --Structure of human secretory immunoglobulin A.
- P50DE-02670-15 0019 (DSR) MILLER, EDWARD J. --Chemistry and molecular biology of the connective tissue protein, collagen.
- P50DE-02670-15 0020 (DSR) NAVIA, JUAN M. --Nutrition--Disease proneness during dental development.
- P50DE-02670-15 0024 (DSR) RODEN, LENNART. --Metabolism of connective tissue proteoglycans.
- P50DE-02670-15 0025 (DSR) SHIOTA, TETSUO. --Biochemical basis for the cariogenic property of *Streptococcus mutans* (rat).
- P50DE-02670-15 0029 (DSR) BAKER, JOHN R. --Structure of connective tissue proteoglycans (cattle).
- P50DE-02670-15 0033 (DSR) CURTISS, ROY. --Genetic and biochemical basis for *S. mutans* virulence (rats).
- P50DE-02670-15 0035 (DSR) PARMLEY, RICHARD T. --Granulocyte growth and division.
- P50DE-02670-15 0036 (DSR) RETIEF, D HUGO. --Varnish and trace elements effects on enamel fluoride and dental caries (rats).
- P50DE-02670-15 0037 (DSR) MCGHEE, JERRY R. --Cellular basis of induction of secretory immune response (mice).
- P50DE-02731-15 (DSR) AVERY, JAMES K, UNIVERSITY OF MICHIGAN, 1011 NORTH UNIVERSITY AVENUE, ANN ARBOR, MICH 48109 Development support for dental research institute.
- P50DE-02731-15 0001 (DSR) ASH, MAJOR M. Development support for dental research institute--Functional disturbances of the masticatory system (human).
- P50DE-02731-15 0019 (DSR) CLEWELL, DON B. Development support for dental research institute--Structure and maintenance of extrachromosomal DNA in streptococci.
- P50DE-02731-15 0021 (DSR) LOESCHE, WALTER J. Development support for dental research institute--Bacterial specificity in periodontal disease.
- P50DE-02731-15 0031 (DSR) DZIEWIATKOWSKI, DONIMIC D. Development support for dental research institute--Chemistry and physiology of proteoglycans and collagen of connective tissues.
- P50DE-02731-15 0032 (DSR) MACCALLUM, DONALD K. Development support for dental research institute--Epithelial cell basal lamina biosynthesis (rats).
- P50DE-02731-15 0033 (DSR) RAMFJORD, SIGURD P. Development support for dental research institute--Clinical trials of periodontal therapy.
- P50DE-02731-15 0035 (DSR) LOPATIN, DENNIS E. Development support for dental research institute--Immune regulation in periodontal disease.
- P50DE-02731-15 0036 (DSR) HIGUCHI, WILLIAM I. Development support for dental research institute--Optimal methods of enamel remineralization.
- P50DE-02731-15 0037 (DSR) OBRIEN, W J. Development support for dental research institute--Luminescence and polarized light in the diagnosis and treatment of caries.
- P50DE-02731-15 0038 (DSR) FLYNN, GORDON L. Development support for dental research institute--Antiviral chemotherapy--Drug delivery component.
- R01DE-02774-13 (OBM) BRINKLEY, LINDA L, UNIVERSITY OF MICHIGAN, 1335 CATHERINE ST, ANN ARBOR, MICH 48109 Tissue interaction in palatal shelf closure (mice).
- P01DE-02847-13 (SSS) GIBBONS, RONALD J, FORSYTH DENTAL CENTER, 140 FENWAY, BOSTON, MASS 02115 Microbial ecology and its relation to dental disease.
- P01DE-02847-13 0020 (SSS) GIBBONS, RONALD J. Microbial ecology and its relation to dental disease--Acquisition transmission and localization of human oral bacteria.
- P01DE-02847-13 0021 (SSS) VANHOUTE, JOHANNES. Microbial ecology and its relation to dental disease--Acquisition, transmission and localization of human oral bacteria (rodents).
- P01DE-02847-13 0022 (SSS) JORDAN, HAROLD V. Microbial ecology and its relation to dental disease--Cemental caries as a dental problem (human, rats, primates).
- P01DE-02847-13 0023 (SSS) SOCRANSKY, SIGMUND S. Microbial ecology and its relation to dental disease--Microbiota associated with periodontal diseases (human, rats, hamsters).
- P01DE-02848-11 (SSS) SLAVKIN, HAROLD C, UNIV OF SOUTHERN CALIFORNIA, LAB FOR DEVELOPMENTAL BIOLOGY, LOS ANGELES, CALIF 90007 Biology of connective tissue, bones, and teeth.
- P01DE-02848-11 0001 (SSS) SLAVKIN, HAROLD C. Biology of connective tissue, bones, and teeth--Mesenchymal interactions (mice, rabbit).
- P01DE-02848-11 0002 (SSS) SLAVKIN, HAROLD C. Biology of connective tissue, bones, and teeth--Steroid receptors in craniofacial teratology (mice).
- P01DE-02848-11 0003 (SSS) SLAVKIN, HAROLD C. Biology of connective tissue, bones, and teeth--Mandibular morphogenesis--Embryonic neonatal and postnatal development (mice).
- P01DE-02848-11 0004 (SSS) BROWNELL, A G. Biology of connective tissue, bones, and teeth--Embryonic basal lamina development.
- P01DE-02872-12 (SSS) PRUZANSKY, SAMUEL, P O BOX 6998, CHICAGO, ILL 60680.
- P01DE-02872-12 0018 (SSS) PRUZANSKY, P. --Date bank--Computerization of clinical data.
- P01DE-02872-12 0034 (SSS) PRUZANSKY, SAMUEL. --Digitization of roentgencephalometric data (human).
- P01DE-02872-12 0035 (SSS) PRUZANSKY, SAMUEL. --Natural history of cleft lip and palate--Morphoanalysis.

- P01DE-02872-12 0036 (SSS) PRUZANSKY, SAMUEL. --Natural history of cleft lip and palate--Malocclusion.
- P01DE-02872-12 0037 (SSS) PRUZANSKY, SAMUEL. --Natural history of cleft lip and palate--Maxillary arch.
- P01DE-02872-12 0038 (SSS) PRUZANSKY, SAMUEL. --Evaluation of craniofacial surgery.
- P01DE-02872-12 0053 (SSS) GOLD, H O. --Maxillofacial prosthetics (human).
- P01DE-02872-12 0055 (SSS) KAYE, C. --Human genetics.
- P01DE-02872-12 0056 (SSS) PARRIS, PAMELA. --Center for craniofacial anomalies.
- P01DE-02872-12 0057 (SSS) PETERSON-FALZONE, SALLY J. --Speech and hearing testing (human).
- P01DE-02872-12 0058 (SSS) MILLER, MARILYN. --Ophthalmology (human, rabbits).
- P01DE-02872-12 0059 (SSS) ROWLATT, V. --Necessary studies--Gross and microscopic.
- P01DE-02872-12 0060 (SSS) WOLKE, IRA. --Sensory deficits in otocraniofacial syndromes.
- P01DE-02872-12 0061 (SSS) PRUZANSKY, SAMUEL. --Craniofacial dysmorphology.
- P01DE-02872-12 0062 (SSS) PRUZANSKY, SAMUEL. --Congenital palatopharyngeal incompetence.
- P01DE-02872-12 0063 (SSS) PRUZANSKY, SAMUEL. --Premature craniofacial synostoses (human).
- P01DE-02872-12 9001 (SSS) PRUZANSKY, SAMUEL. --Core.
- R01DE-02873-14 (OBM) MOORREES, COENRAAD F, FORSYTH DENTAL CENTER, 140 FENWAY, BOSTON, MASS 02115 Facial and dental growth in pre- and post-adolescents (twins).
- R01DE-02901-13 (ALY) BLEIWEIS, ARNOLD S, UNIVERSITY OF FLORIDA, 1053 MC CARTY HALL, GAINESVILLE, FLA 32611 Cell wall antigens of cariogenic streptococci (human, rabbits).
- R01DE-02936-13 (OBM) MAHLER, DAVID B, 611 S W CAMPUS DRIVE, PORTLAND, OREG 97201 Marginal fracture of dental amalgam.
- R01DE-03118-11 (MBC) SMITH, ERIC E, UNIVERSITY OF MIAMI, DEPT OF BIOCHEMISTRY, MIAMI, FLA 33136 Inhibition of saccharide metabolism by oral flora.
- R01DE-03180-11 (BM) ROSAN, BURTON, UNIVERSITY OF PENNSYLVANIA, 4001 SPRUCE STREET, PHILADELPHIA, PA 19174 Microbiologic studies of the human oral streptococci.
- R01DE-03187-10 (OBM) MORENO, EDGARD C, FORSYTH DENTAL CENTER, 140 THE FENWAY, BOSTON, MASS 02115 Transport in enamel and solubility of fluoridated apatites (human).
- R01DE-03223-11 (OBM) NANCOLLAS, GEORGE H, S U N Y - AT BUFFALO, DEPT OF CHEMISTRY, BUFFALO, N Y 14214 Kinetics of mineralization of teeth (human).
- R01DE-03246-12 (CBY) CAPLOW, MICHAEL, UNIVERSITY OF NORTH CAROLINA, DEPARTMENT OF BIOCHEMISTRY, CHAPEL HILL, N C 27514 Biochemical mechanisms relevant to dentistry (bacteria).
- R01DE-03258-10 (OBM) KURAMITSU, HOWARD K, NORTHWESTERN UNIVERSITY, 303 E CHICAGO AVENUE, CHICAGO, ILL 60611 *Streptococcus mutans*--Dental caries mechanism (human).
- R01DE-03301-11 (PBC) PAGE, ROY C, UNIVERSITY OF WASHINGTON, DEPARTMENT OF PATHOLOGY SM-30, SEATTLE, WASH 98195 Connective tissue of the periodontium--Collagen maturation.
- R01DE-03318-10 (PBC) SCHNEIR, MICHAEL I, UNIV OF SOUTHERN CALIFORNIA, DEPARTMENT OF BASIC SCIENCES, LOS ANGELES, CALIF 90007 The molecular nature of gingival and mucosal collagen (rat).
- R01DE-03408-09 (OBM) NISENGARD, RUSSELL J, S U N Y - AT BUFFALO, 3435 MAIN STREET, BUFFALO, N Y 14214 Immunopathology of gingivitis and periodontitis (monkeys, human).
- R01DE-03420-09 (OBM) TAUBMAN, MARTIN A, FORSYTH DENTAL CENTER, 140 FENWAY, BOSTON, MASS 02115 Immune phenomena in experimental periodontal disease (rats).
- R01DE-03469-10 (HED) ZIMMERMAN, ERNEST F, CHILDREN'S HOSPITAL, ELLAND AND BETHESDA AVENUES, CINCINNATI, OHIO 45229 Teratogens effects on cleft palate formation (mice).
- R01DE-03487-10 (BM) SHOCKMAN, GERALD D, TEMPLE UNIVERSITY, DEPT OF MICROBIOL/IMMUNOLOGY, PHILADELPHIA, PA 19140 Inhibition of human cariogenic streptococci.
- R01DE-03488-10 (OBM) SOCRANSKY, SIGMUND S, FORSYTH DENTAL CENTER, 140 THE FENWAY, BOSTON, MASS 02115 Microbial composition of developing dental plaque.
- R01DE-03497-09 (OBM) YOUNG, FRANKLIN A, JR, MEDICAL UNIV OF SOUTH CAROLINA, 171 ASHLEY AVENUE, CHARLESTON, S C Artificial tooth roots (Rhesus monkeys, human).
- R01DE-03545-09 (OBM) BURSTONE, CHARLES J, UNIVERSITY OF CONNECTICUT, DEPARTMENT OF ORTHODONTICS, FARMINGTON, CONN 06032 Prediction of tooth displacement (human).
- P01DE-03568-07 (SSS) CONVERSE, JOHN M, NEW YORK UNIVERSITY MED CTR, 550 FIRST AVENUE, NEW YORK, N Y 10016.
- P01DE-03568-07 0008 (SSS) MCCARTHY, JOSEPH G. --Craniofacial growth.
- P01DE-03568-07 0009 (SSS) MCCARTHY, JOSEPH G. --Cephalometrics.
- P01DE-03568-07 0013 (SSS) MCCARTHY, JOSEPH G. --Pedodontics.
- R01DE-03578-10 (PC) ROBYT, JOHN F, IOWA STATE UNIVERSITY, DEPT BIOCHEMISTRY & BIOPHYSICS, AMES, IOWA 50011 Biosynthetic study of dental plaque polysaccharides.
- R01DE-03598-07 (OBM) BAUMRIND, SHELDON, UNIVERSITY OF CALIFORNIA, DEPT OF GROWTH & DEVELOPMENT, SAN FRANCISCO, CALIF 94143 Ontofacial effects of forces to retract the maxilla (human).
- R01DE-03601-09 (OBM) MAREK, MIROSLAV, GEORGIA INST OF TECHNOLOGY, SCHOOL OF CHEMICAL ENGINEERING, ATLANTA, GA 30332 Localized corrosion of dental amalgam.
- P01DE-03610-15 (SSS) MOYERS, ROBERT E, UNIVERSITY OF MICHIGAN, 1111 EAST CATHERINE STREET, ANN ARBOR, MICH 48109.
- P01DE-03610-15 0016 (SSS) MOYERS, ROBERT E. --Craniofacial shape change and oral development.
- P01DE-03610-15 0017 (SSS) BURDI, ALPHONSE R. --Craniofacial profile patterns in normal and malformed prenatals and postnates.
- P01DE-03610-15 0018 (SSS) MCNAMARA, JAMES A. --Function and growth of the temporomandibular joint (monkeys).

** SEE GLOSSARY OF ABBREVIATIONS for explanation of grant and contract number

PROJECT NO., REVIEW GROUP, INVESTIGATOR, ADDRESS, AND TITLE

PROJECT NO., REVIEW GROUP, INVESTIGATOR, ADDRESS, AND TITLE

- R01DE-03619-09 (OBM) DAVIDOVITCH, ZEEV**, 4001 SPRUCE STREET, PHILADELPHIA, PA 19104 Biochemistry of tooth eruption, movement and resorption (cats).
- R01DE-03631-08 (CMS) HAMLET, SANDRA L**, UNIVERSITY OF MARYLAND, DEPARTMENT HEARING & SPEECH, COLLEGE PARK, MD 20742 Physiological study of speech adaptation (human).
- R01DE-03654-09 (OBM) SCHACHTELE, CHARLES F**, UNIVERSITY OF MINNESOTA, SCHOOL OF DENTISTRY, MINNEAPOLIS, MINN 55455 Molecular basis of dental caries (human).
- R01DE-03658-17 (MGN) AZEN, EDWIN A**, UNIVERSITY OF WISCONSIN, 1300 UNIVERSITY AVENUE, MADISON, WIS 53706 Genetic polymorphisms of saliva (human).
- R01DE-03666-07 (RAD) SODICOFF, MARVIN**, TEMPLE UNIVERSITY, 3400 N BROAD STREET, PHILADELPHIA, PA 19140 X-ray therapeutic index for salivary glands.
- R01DE-03703-05 (OBM) BAUMRIND, SHELDON**, UNIVERSITY OF CALIFORNIA, DEPT OF GROWTH AND DEVELOPMENT, SAN FRANCISCO, CALIF 94143 Integrated three-dimensional craniofacial measurement (human).
- R01DE-03713-06 (OBM) HANDELMAN, STANLEY L**, EASTMAN DENTAL CENTER, 625 ELMWOOD AVENUE, ROCHESTER, N Y 14620 Effect of fissure sealant on progress of dental caries (human).
- R01DE-03715-06 (PC) ROSSOMANDO, EDWARD F**, UNIVERSITY OF CONNECTICUT, DEPARTMENT OF ORAL BIOLOGY, FARMINGTON, CONN 06032 Cellular assembly—its role in facial morphogenesis (fungi).
- R01DE-03731-06 (PC) MAYER, ROBERT M**, OHIO STATE UNIVERSITY, 140 W 18TH AVENUE, COLUMBUS, OHIO 43210 Oextran sucrose of *Streptococcus sanguis*.
- R01DE-03738-09 (EI) SNYDERMAN, RALPH**, DUKE UNIVERSITY, POST OFFICE BOX 3892, DURHAM, N C 27710 Humoral and cellular mediators of inflammation (human, animals).
- R01DE-03739-09 (OBM) MOOSER, GREGORY**, UNIVERSITY OF SOUTHERN CALIF, PO BOX 77951, LOS ANGELES, CALIF 90007 Glycosyltransferases from oral bacteria (bacteria).
- R01DE-03745-10 (OBM) GARANT, PHILIP R**, S U N Y - AT STONY BROOK, ORAL BIOLOGY & PATHOLOGY DEPT, STONY BROOK, N Y 11794 Ultrastructure of experimental periodontitis (rats).
- R01DE-03758-07 (OBM) FREEDMAN, MICHAEL L**, UNIVERSITY OF CONNECTICUT, DEPARTMENT OF ORAL DIAGNOSIS, FARMINGTON, CONN 06032 Virulence characterization and immunization against *S* mutants (rats, rabbits).
- R01DE-03780-09 (OBM) PASHLEY, DAVID H**, MEDICAL COLLEGE OF GEORGIA, LANEY WALKER BLVD, AUGUSTA, GA 30912 Permeability characteristics of dentin (dogs, human).
- R01DE-03794-09 (OBM) BELL, WILLIAM H**, UNIVERSITY OF TEXAS, 5323 HARRY HINES BOULEVARD, DALLAS, TEX 75235 Surgical-orthodontics and bone healing (monkeys).
- R01DE-03818-08 (OBM) MARKS, SANDY C, JR**, UNIVERSITY OF MASSACHUSETTS, 55 LAKE AVENUE, WORCESTER, MASS 01605 Role of the osteoclast in tooth eruption (rats).
- R01DE-03856-07 (OBM) SHEARER, THOMAS R**, UNIVERSITY OF OREGON, 611 S W CAMPUS DRIVE, PORTLAND, OREG 97201 Fluoride-selenium interaction in dental caries (rats).
- R01DE-03915-08 (OBM) HAY, DONALD I**, FORSYTH DENTAL CENTER, 140 FENWAY, BOSTON, MASS 02115 Tooth-saliva interface phenomena and dental caries (rabbits, goats).
- R01DE-03934-07 (OBM) FARBMAN, ALBERT I**, NORTHWESTERN UNIVERSITY, 303 EAST CHICAGO AVENUE, CHICAGO, ILL 60611 Differentiation of oral epithelium (rats).
- R01DE-03953-07 (OBM) BURSTONE, CHARLES J**, UNIVERSITY OF CONNECTICUT, FARMINGTON, CONN 06032 Force systems from orthodontic appliances.
- R01DE-03965-08 (OBM) JOHNSON, LEWIS B**, UNIVERSITY OF VIRGINIA, DEPT OF MATERIALS SCIENCE, CHARLOTTESVILLE, VA 22901 Dental alloy with small additions of other materials.
- R01DE-03987-07 (OBM) GOLUB, LORNE M**, STATE UNIVERSITY OF NEW YORK, STONY BROOK, NEW YORK 11794 Gingival collagen metabolism in health and disease (human, rats).
- R01DE-03991-06 (SB) NATIELLA, JOSEPH R**, S U N Y - AT BUFFALO, 3435 MAIN STREET, BUFFALO, N Y 14214 Cryosurgical techniques applied to malignant melanoma.
- R01DE-03993-07 (OBM) KLEINBERG, ISRAEL**, S U N Y - AT STONY BROOK, DEPT OF ORAL BIOLOGY & PATH, STONY BROOK, N Y 11794 Effect of saliva on the metabolism of dental plaque.
- R01DE-03995-07 (OBM) TAICHMAN, NORTON S**, UNIVERSITY OF PENNSYLVANIA, 4001 SPRUCE STREET, PHILADELPHIA, PA 19104 Leukocytes in the pathogenesis of periodontal disease (human, mice).
- R01DE-03996-06 (RAD) LURIE, ALAN G**, UNIVERSITY OF CONNECTICUT, 263 FARMINGTON AVENUE, FARMINGTON, CONN 06032 Low level irradiation—modification of carcinogenesis.
- R01DE-04004-07 (BEM) CHAPMAN, C RICHARD**, UNIVERSITY OF WASHINGTON, BB1437, MAIL STOP RN-10, SEATTLE, WASH 98195 Acupuncture and perception of dental pain (human).
- R01DE-04008-07 (GMB) CAPLAN, ARNOLD I**, CASE WESTERN RESERVE UNIV, DEPARTMENT OF BIOLOGY, CLEVELAND, OHIO 44106 Cellular and developmental control of calcification (tissue culture).
- R01DE-04039-04 (OBM) VITTEK, JOZEF**, NEW YORK MEDICAL COLLEGE, VALHALLA, N Y 10595 Sex steroid metabolism in oral tissues.
- R01DE-04047-05 (OBM) WEINSTEIN, SAM**, UNIVERSITY OF CONNECTICUT, SCHOOL OF DENTAL MEDICINE, FARMINGTON, CONN 06032 Extensibility characteristics of human cheek.
- R01DE-04061-07 (OBM) EVANS, RICHARD T**, S U N Y - AT BUFFALO, 4510 MAIN STREET, BUFFALO, N Y 14226 Salivary antibodies to *S* mutants—Induction and effects (monkeys).
- R01DE-04068-07 (EDC) FLEISS, JOSEPH L**, COLUMBIA UNIVERSITY, 600 WEST 168TH STREET, NEW YORK, N Y 10032 Statistical methods in dental research.
- R01DE-04096-05 (OBM) LANGELAND, KAARE**, UNIVERSITY OF CONNECTICUT, DEPARTMENT OF ENDODONTICS, FARMINGTON, CONN 06032 Biocompatibility of endodontic materials (animals).
- R01DE-04101-07 (OBM) LEINFELDER, KARL F**, UNIVERSITY OF NORTH CAROLINA, POST OFFICE BOX 750, CHAPEL HILL, N C 27514 Corrosion of precious metal alloys (human).
- R01DE-04125-06 (OBM) DABBOUS, MUSTAFA K**, UNIVERSITY OF TENNESSEE, 800 MADISON AVENUE, MEMPHIS, TENN 38163 Gingival matrix proteins and periodontal disease (human, mammals).
- R01DE-04136-07 (OBM) KORAN, ANDREW, III**, UNIVERSITY OF MICHIGAN, 1011 N UNIVERSITY AVENUE, ANN ARBOR, MICH 48109 Maxillofacial materials—Color study.
- R01DE-04141-07 (OBM) BOSKEY, ADELE L**, HOSPITAL FOR SPECIAL SURGERY, 535 EAST 70TH ST, NEW YORK, N Y 10021 Mechanism of hard tissue mineralization (human, rats).
- R01DE-04157-08 (OBM) GIBBS, CHARLES H**, UNIVERSITY OF FLORIDA, BOX J-424, JHMHC, GAINESVILLE, FLA 32610 Functional mandibular movements (human).
- R01DE-04164-06 (OBM) MUHL, ZANE F**, UNIVERSITY OF ILLINOIS, 801 S PAULINA ST, CHICAGO, ILL 60612 Functional properties of mammalian masticatory muscles.
- R01DE-04174-07 (OBM) KNOX, KENNETH W**, UNITED DENTAL HOSPITAL, CHALMERS STREET, SURRY HILLS, N S W 2010, AUSTRALIA Variations in the surface structures of oral bacteria.
- R01DE-04175-07 (OBM) WICKEN, ANTHONY J**, UNIVERSITY OF NEW SOUTH WALES, PO BOX 1 KENSINGTON, NSW 2033, AUSTRALIA Variations in the surface structures of oral bacteria.
- R01DE-04192-07 (OBM) JORDAN, TRUMAN H**, CORNELL COLLEGE, MOUNT VERNON, IOWA 52314 SnF₂-Ca (OH) 2-H3O4-H2O reaction system.
- R01DE-04217-07 (OBM) MC GHEE, JERRY R**, UNIVERSITY OF ALABAMA, UNIVERSITY STATION, BIRMINGHAM, ALA 35294 Effective immunity to dental caries—Cellular basis.
- R01DE-04224-07 (GEN) MACRINA, FRANCIS L**, VIRGINIA COMMONWEALTH UNIV, BOX 678-MCV STATION, RICHMOND, VA 23298 Genetics of oral microflora.
- R01DE-04227-07 (OBM) MC NAMARA, JAMES A, JR**, UNIVERSITY OF MICHIGAN, 1111 E CATHERINE STREET, ANN ARBOR, MICH 48109 Adaptations to changes in masticatory muscle length (monkeys).
- R01DE-04230-07 (OBM) SKOBE, ZIEDONIS**, FORSYTH DENTAL CENTER, 140 FENWAY, BOSTON, MASS 02115 Comparative ultrastructure of mammalian amelogenesis (human, mammals).
- R01DE-04235-06 (SSS) THOMAS, EDWIN L**, ST JUDE CHILDREN'S RES HOSP, 332 NORTH LAUDERDALE, MEMPHIS, TENN 38101 Peroxidase in saliva and prevention of oral disease (human, *S* mutants).
- R01DE-04252-07 (SSS) FAIRHURST, CARL W**, MEDICAL COLLEGE OF GEORGIA, SCHOOL OF DENTISTRY, AUGUSTA, GA 30912 Semi and nonprecious metal-porcelain systems.
- R01DE-04257-05 (CBY) LE DOUARIN, NICOLE M**, COLLEGE DE FRANCE, 49BIS AVE DE LA BELLE-GABRIELLE, 94130 NOGENT-SUR-MARNE FRANCE Migration and differentiation of neural crest cells (quail, chick embryo, mi).
- R01DE-04262-07 (OBM) OKABE, TORU**, MEDICAL COLLEGE OF GEORGIA, SCHOOL OF DENTISTRY, AUGUSTA, GA 30912 Amalgamation kinetics on Ag-Sn (X) alloys.
- R01DE-04278-06 (OBM) COWMAN, RICHARD A**, VETERANS ADMINISTRATION HOSP, 1201 N W 16TH STREET, MIAMI, FLA 33125 Human saliva-streptococcal metabolic interactions.
- R01DE-04296-07 (OBM) POLLOCK, JERRY J**, S U N Y - AT STONY BROOK, DEPT OF ORAL BIOLOGY, STONY BROOK, N Y 11794 Lysozyme—Cell surface interactions and oral defense.
- R01DE-04316-05 (CBY) WESTON, JAMES A**, UNIVERSITY OF OREGON, DEPARTMENT OF BIOLOGY, EUGENE, OREG 97403 Extracellular matrix and morphogenesis in mutant mice (also birds).
- R01DE-04321-07 (OBM) MC CABE, MEAD M**, UNIVERSITY OF MIAMI, PO BOX 016960, MIAMI, FLA 33101 Cell adherence of dental plaque forming streptococci (rabbits).
- R01DE-04327-06 (GMB) RODAN, GIDEON A**, UNIVERSITY OF CONNECTICUT, HLTH, DEPT OF ORAL BIOLOGY, FARMINGTON, CONN 06032 Mechanical and electrical effects on osteogenesis (chick embryo).
- R01DE-04332-06 (OBM) WHITFORD, GARY M**, MEDICAL COLLEGE OF GEORGIA, RESEARCH & EDUC BLDG, AUGUSTA, GA 30912 Influence of acid-base status on fluoride metabolism (rats, dogs).
- R01DE-04335-05 (OBM) OPPERBECK, WILLIAM R**, NEW JERSEY DENTAL SCHOOL, 100 BERGEN STREET, NEWARK, N J 07103 Comparison of treatment procedures used in endodontics.
- R01DE-04338-06 (GMA) OCCHINO, JOSEPH C**, CASE WESTERN RESERVE UNIV, 2123 ABINGTON ROAD, CLEVELAND, OHIO 44108 Characterization of oral mucosa and skin basal lamina (human, animals).
- R01DE-04345-06 (OBM) SCHRAER, HAROLD**, PENNSYLVANIA STATE UNIVERSITY, 517 MUELLER BUILDING, UNIVERSITY PARK, PA 16802 Cellular and molecular aspects of mineralization (chick embryo).
- R01DE-04358-06 (EDC) GALE, ELLIOT N**, 4510 MAIN STREET, DEPT OF BEHAVIORAL SCIENCE, BUFFALO, N Y 14226 Treatment of temporomandibular joint pain.
- R01DE-04385-06 (OBM) BROWN, WALTER E**, AMERICAN DENTAL ASSOC HLTH FDN, 211 EAST CHICAGO AVENUE, CHICAGO, ILL 60611 Mechanism of dental caries (human).
- R01DE-04387-05 (OBM) ALLMANN, DAVID W**, INDIANA UNIVERSITY, 1100 WEST MICHIGAN STREET, INDIANAPOLIS, IND 45223 Effect of fluoride on CAMP and glucose metabolism.
- R01DE-04394-05 (OBM) FAIRHURST, CARL W**, MEDICAL COLLEGE OF GEORGIA, DEPT OF RESTORATIVE DENT, AUGUSTA, GA 30902 Pin and slot retention in amalgam and composite materials.
- R01DE-04414-06 (OBM) SPECTOR, MYRON**, UNIVERSITY OF SOUTH CAROLINA, 171 ASHLEY AVENUE, CHARLESTON, S C 29403 Porous high density polyethylene tooth roots (monkeys).
- R01DE-04439-04 (OBM) VOGEL, JAMES J**, UNIV OF TEXAS DENTAL BRANCH, PO BOX 20068, HOUSTON, TX 77025 Dental calculus formation using calculable lipoprotein analogues.
- R01DE-04475-04 (OBM) MESSER, HAROLD H**, UNIVERSITY OF MINNESOTA, SCHOOL OF DENTISTRY, MINNEAPOLIS, MINN 55455 Mineral nutrition and alveolar bone loss (mice).
- R01DE-04486-04 (OBM) WEFEL, JAMES S**, UNIVERSITY OF IOWA, DOWS INST FOR DENTAL RESEARCH, IOWA CITY, IOWA 52242 Kinetics and mechanisms of action of fluorides.

** SEE GLOSSARY OF ABBREVIATIONS for explanation of grant and contract number

- R01DE-04487-05 (OBM) SHAPIRO, EVERETT**, TUFTS UNIVERSITY, DEPARTMENT OF ORTHODONTICS, BOSTON, MASS 02111 Pulsating forces in orthodontics (human).
- R01DE-04489-06 (OBM) RIVIERE, GEORGE R**, UNIVERSITY OF CALIFORNIA, SCHOOL OF DENTISTRY, LOS ANGELES, CALIF 90024 Tooth transplantation genetics and immunology (mice, monkeys).
- R01DE-04494-05 (EDC) CORAH, NORMAN L**, 4510 MAIN STREET, DEPT OF BEHAVIORAL SCIENCE, BUFFALO, N Y 14226 Control of stress during dental procedures (human).
- R01DE-04501-06 (OBM) MACEDO-SOBRINHO, BRAZ**, COLLEGE OF NEW JERSEY, 100 BERGEN STREET, NEWARK, N J 07103 Cell mediated immunity in gingival inflammation (mice).
- R01DE-04504-03 (OBM) BURT, BRIAN A**, UNIVERSITY OF MICHIGAN, SCHOOL OF PUBLIC HEALTH, ANN ARBOR, MICH 48109 Plaque bacteria as predictors of human dental caries.
- R01DE-04511-06 (OBM) TAICHMAN, LORNE B**, S U N Y AT STONY BROOK, SCHOOL OF DENTAL MEDICINE, STONY BROOK, N Y 11794 Stability of differentiation-Craniofacial study (human, hamsters).
- R01DE-04516-03 (OBM) RYGE, GUNNAR**, UNIVERSITY OF THE PACIFIC, 2155 WEBSTER STREET, SAN FRANCISCO, CALIF 94115 Corrosion and clinical behavior of dental amalgam.
- R01DE-04517-03 (OBM) HAGERTY, ROBERT F**, ST FRANCIS XAVIER HOSPITAL, 150 ASHLEY AVE, CHARLESTON, S C 29401 Pin-retained prosthesis with surgery in cleft palate.
- R01DE-04518-06 (OBM) LEVINE, MICHAEL J**, S U N Y - AT BUFFALO, 4510 MAIN STREET, BUFFALO, N Y 14226 Streptococcus sanguis receptors for salivary glycoproteins.
- R01DE-04529-05 (OBM) HILLMAN, JEFFREY D**, FORSYTH DENTAL CENTER, 140 FENWAY, BOSTON, MASS 02115 Replacement therapy of dental caries (rats, monkeys).
- R01DE-04531-04 (OBM) HYLANDER, WILLIAM L**, DUKE UNIVERSITY MEDICAL CENTER, DEPARTMENT OF ANATOMY, DURHAM, N C 27710 Strain in the facial bones of (primates).
- R01DE-04600-04 (OBM) FOX, JEFFREY L**, UNIVERSITY OF MICHIGAN, COLLEGE OF PHARMACY, ANN ARBOR, MICH 48109 Hydroxyapatite remineralization--Role of fluoride.
- R01DE-04610-03 (OBM) GAY, THOMAS J**, UNIVERSITY OF CONNECTICUT, DEPT OF ORAL BIOLOGY, FARMINGTON, CONN 06032 Physiological studies on mastication (human).
- R01DE-04614-05 (OBM) LILJEMARK, WILLIAM F**, UNIVERSITY OF MINNESOTA, 515 DELAWARE STREET S E, MINNEAPOLIS, MINN 55455 Adherence of oral streptococci to hydroxyapatite.
- R01DE-04615-04 (OBM) WHANGER, PHILIP D**, OREGON STATE UNIVERSITY, DEPT OF AGRICULTURAL CHEMISTRY, CORVALLIS, OREG 97331 Fluoride-cadmium interaction in dental caries (rats, human).
- R01DE-04616-04 (OBM) SHEARER, THOMAS R**, UNIV OF OREGON HLTH SCI SCTR, 611 S W CAMPUS DRIVE, PORTLAND, OREG 97201 Fluoride-cadmium interaction in dental caries (rats).
- R01DE-04622-05 (HED) GOLDMAN, ALLEN S**, JOSEPH STOKES, JR RES INST, 34TH STREET & CIVIC CTR BLVD., PHILADELPHIA, PA 19104 Craniofacial anomalies and protein receptors (mice, human).
- R01DE-04629-05 (OBM) KAHN, ARNOLD J**, WASHINGTON UNIVERSITY, 4559 SCOTT AVENUE, ST LOUIS, MO 63110 Dental disease and osteoclastic bone resorption (chick embryo, quail).
- R01DE-04645-04 (MBC) CHARON, NYLES W**, WEST VIRGINIA UNIVERSITY, DEPARTMENT OF MICROBIOLOGY, MORGANTOWN, W VA 26506 A genetic-biochemical analysis of spirochete motility.
- R01DE-04657-05 (PBC) ROSSOMANDO, EDWARD F**, UNIVERSITY OF CONNECTICUT, DEPARTMENT OF ORAL BIOLOGY, FARMINGTON, CONN 06032 Abnormal palatal development induced by hadacidin (fungi).
- R01DE-04660-06 (GMA) DALE, BEVERLY A**, UNIVERSITY OF WASHINGTON, DEPARTMENT OF PERIODONTICS, SEATTLE, WASH 98195 Keratohyalin in keratinization--Oral mucosa and skin (human).
- R01DE-04704-05 (OBM) MARSHALL, SALLY J**, NORTHWESTERN UNIV DENTAL SCH, 311 E CHICAGO AVE, CHICAGO, ILL 60611 X-ray and sem analysis of CU rich dental amalgam.
- R01DE-04705-03 (OBM) JORDAN, TRUMAN H**, CORNELL COLLEGE, MT VERNON, IOWA 52314 Reactions of titanium fluoride with hydroxyapatite.
- R01DE-04721-04 (OBM) COTEKENDALL, ALAN L**, UNIVERSITY OF CONNECTICUT, DEPARTMENT OF ORAL DIAGNOSIS, FARMINGTON, CONN 06032 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs).
- R01DE-04731-05 (HED) MINKOFF, ROBERT**, UNIVERSITY OF NORTH CAROLINA, DEPARTMENT OF ORTHODONTICS, CHAPEL HILL, N C 27514 Analysis of primary palate formation (chick embryo).
- R01DE-04744-04 (OBM) COBURN, ROBERT A**, S U N Y AT BUFFALO, DEPT OF MEDICINAL CHEMISTRY, BUFFALO, N Y 14260 New antimicrobial agents for preventing oral diseases.
- R01DE-04779-04 (OBM) STARR, PHILIP**, H K COOPER INSTITUTE, 24 NORTH LIME STREET, LANCASTER, PA 17602 Behavioral stages for cleft palate patients.
- R01DE-04781-02 (OBM) KROGMAN, WILTON M**, H K COOPER CLINIC, 24 NORTH LIME STREET, LANCASTER, PA 17602 Serial craniofacial growth in clefting--Birth to fifteen years.
- R01DE-04783-04 (RAD) KAPLAN, JEROME I**, 909 WEST NEW YORK STREET, INDIANAPOLIS, IND 46202 The development of a dental x-ray aiming device.
- R01DE-04786-04 (BPO) SESSLE, BARRY J**, UNIVERSITY OF TORONTO, 124 EDWARD ST, TORONTO, ONT, CANADA M5G 1G6 Dental and orofacial pain--Brain stem mechanisms (cats).
- R01DE-04795-05 (OBM) MINAH, GLENN E**, UNIVERSITY OF MARYLAND, 666 W BALTIMORE STREET, BALTIMORE, MD 21201 Characteristics of cariogenic dental plaque.
- R01DE-04808-02 (BM) SLEE, ANDREW M**, UNIVERSITY OF CONNECTICUT, DEPARTMENT OF ORAL DIAGNOSIS, FARMINGTON, CONN 06032 Virulence factors of gram negative corroding bacteria.
- R01DE-04814-02 (OBM) MAY, PAUL D**, GULF SOUTH RESEARCH INST, POST OFFICE BOX 26518, NEW ORLEANS, LA 70186 New polymers for permanent soft denture liners.
- R01DE-04819-05 (OBM) SILVERSTONE, LEON M**, UNIVERSITY OF IOWA, DIVISION OF CARIOLOGY, IOWA CITY, IOWA 52242 Remineralization of enamel caries in vitro (human).
- R01DE-04835-03 (OBM) CLARKSON, BRIAN H**, UNIVERSITY OF IOWA, COLLEGE OF DENTISTRY, IOWA CITY, IOWA 52242 Anti-caries mechanism of fluoride complexes in vitro (human).
- R01DE-04844-04 (OBM) KING, GREGORY J**, UNIVERSITY OF FLORIDA, DEPT OF ORTHODONTICS, GAINESVILLE, FLA 32610 Stress-related bone resorption--Mechanisms of action (rats).
- R01DE-04857-02 (OBM) FAULKNER, JOHN A**, UNIVERSITY OF MICHIGAN, MEDICAL SCHOOL, ANN ARBOR, MI 48109 Temporalis flaps in the treatment of facial paralysis (monkeys).
- R13DE-04860-01 (NSS) SCHNITMAN, PAUL A**, HARVARD SCH OF DENTAL MEDICINE, 188 LONGWOOD AVENUE, BOSTON, MASS 02115 Conference--dental implants: benefit or risk.
- R01DE-04862-04 (NTN) NAVIA, JUAN M**, UNIVERSITY OF ALABAMA, UNIVERSITY STATION, BIRMINGHAM, ALA 35294 Nutritional role of vitamin A in bone and teeth (rat).
- P50DE-04881-05 (DSR) SOCRANSKY, SIGMUND S**, FORSYTH DENTAL CENTER, 140 FENWAY, BOSTON, MASS 02115 Center for clinical research in periodontal diseases.
- P50DE-04881-05 0001 (DSR) SOCRANSKY, SIGMUND S**, Center for clinical research in periodontal diseases--Diagnosis and treatment of destructive periodontal diseases.
- P50DE-04881-05 0002 (DSR) SOCRANSKY, SIGMUND S**, Center for clinical research in periodontal diseases--Relationship of subgingival microbiota to the etiology of periodontal diseases.
- P50DE-04881-05 0003 (DSR) STASHANKO, PHILIP**, Center for clinical research in periodontal diseases--Host immunologic response to oral microorganisms.
- P50DE-04881-05 0004 (DSR) GOODSON, J MAX**, Center for clinical research in periodontal diseases--Relation of inflammation mediators to destructive periodontal diseases.
- R01DE-04883-04 (SSS) ASGAR, KAMAL**, UNIVERSITY OF MICHIGAN, DEPARTMENT OF DENTAL MATERIALS, ANN ARBOR, MICH 48109 Nature of alloy systems for crown and bridge restorations (human).
- R01DE-04884-13 (NEUB) LUSCHEI, ERICH S**, UNIVERSITY OF WASHINGTON, DEPT OF PHYSIOLOGY & BIOPHYSICS, SEATTLE, WASHINGTON, 98195 Neural processes in somatic movement (monkeys).
- R01DE-04889-04 (OBM) MC CALL, WILLARD D, JR**, SUNY AT BUFFALO, DEPARTMENT OF ORAL MEDICINE, BUFFALO, N Y 14214 Dental significance of jaw muscle silent periods (human).
- R01DE-04890-03 (OBM) LINDHE, JAN T**, UNIVERSITY OF GOTHENBURG, DEPARTMENT OF PERIODONTOLOGY, FACK, S-400 33 GOTHENBURG, SWE Plaque control-healing following periodontal surgery.
- R01DE-04897-02 (OBM) MARTINEZ, J RICARDO**, UNIVERSITY OF MISSOURI, CHLO HEALTH DEPARTMENT, COLUMBIA, MO 65212 Functional development of salivary glands (rats).
- P50DE-04898-05 (DSR) GENCO, ROBERT J**, S U N Y - AT BUFFALO, 4510 MAIN STREET, BUFFALO, N Y 14226 Periodontal disease research center.
- P50DE-04898-05 0001 (DSR) GENCO, ROBERT J**, Periodontal disease research center--Microbiology (human).
- P50DE-04898-05 0002 (DSR) GENCO, ROBERT J**, Periodontal disease research center--Host response in periodontal disease (human).
- P50DE-04898-05 0003 (DSR) GENCO, ROBERT J**, Periodontal disease research center--Therapy and prevention of periodontal diseases (human).
- P50DE-04898-05 0004 (DSR) GENCO, ROBERT J**, Periodontal disease research center--Periodontal disease and the electromyographic silent period (human).
- R01DE-04903-03 (OBM) BYERS, BENJAMIN R**, UNIVERSITY OF MISSISSIPPI, 2500 NORTH STATE STREET, JACKSON, MISS 39216 Trace metal uptake in cariogenic streptococcus mutants.
- R01DE-04926-04 (OBM) MC INTIRE, FLOYD C**, UNIVERSITY OF COLORADO MED CTR, 4200 EAST NINTH AVENUE, DENVER, COLO 80262 Bacterial coaggregation mechanisms in dental plaque.
- R01DE-04940-04 (OBM) MILLER, ARTHUR J, 3RD AND PARNASSUS, ROOM 747S**, SAN FRANCISCO, CALIF 94143 Muscular disorders in craniofacial malformations (human).
- R01DE-04957-03 (MBC) PIERINGER, RONALD A**, TEMPLE UNIVERSITY SCH OF MED, 3420 N BROAD STREET, PHILADELPHIA, PA 19140 Bacterial metabolites in oral diseases.
- R01DE-04960-03 (OBM) DENNY, PAUL C**, UNIV OF SOUTHERN CALIFORNIA, UNIVERSITY PARK, LOS ANGELES, CALIF 90007 Mechanisms of salivary gland development (mice, rats).
- R01DE-04970-04 (OBM) SCHWARTZ, STEPHEN A**, UNIVERSITY OF CHICAGO, 950 EAST 59TH ST, CHICAGO, ILL 60637 Molecular characterization of odontogenesis by 5-bromodeoxyuridine.
- R01DE-04971-03 (OBM) LEVINE, MICHAEL J**, S U N Y - AT BUFFALO, 4510 MAIN STREET, BUFFALO, N Y 14226 Human salivary antigens--Characterization (monkeys).
- R01DE-04976-04 (BEM) KLEPAC, ROBERT K**, NORTH DAKOTA STATE UNIVERSITY, DEPARTMENT OF PSYCHOLOGY, FARGO, N DAK 58105 Behavioral strategies for reducing dental avoidance (human).
- R01DE-04990-03 (SSS) SHAW, ROBERT E**, UNIVERSITY OF CONNECTICUT, PSYCHOLOGY DEPARTMENT, STORRS, CONN 06268 Normal and abnormal faces (human).
- R23DE-05006-03 (IMS) LAVEN, GEORGE T**, UNIVERSITY OF ALABAMA, UNIVERSITY STATION, BIRMINGHAM, ALA 35294 Maternal malnutrition--Pregnancy immunology (human).
- R01DE-05008-03 (HED) GASSER, DAVID L**, UNIVERSITY OF PENNSYLVANIA, DEPT OF HUMAN GENETICS, PHILADELPHIA, PA 19104 Basis of drug induced cleft palate (rats, mice).
- R01DE-05017-03 (OBM) LINZER, ROSEMARY**, S U N Y, 4510 MAIN STREET, BUFFALO, N Y 14226 Characterization of surface antigens of S mutants.
- R01DE-05024-03 (OBM) IORIO, ROBERT J**, MARQUETTE UNIVERSITY, 604 N 16TH STREET, MILWAUKEE, WIS 53233 Craniofacial abnormalities in mice with vitamin E resistant rickets.
- R01DE-05027-04 (OBM) TOTIS, WILLIAM W**, LOYOLA UNIVERSITY OF CHICAGO, 2160 SOUTH FIRST AVENUE, MAYWOOD, ILL 60153 Binding of fluoride by cariogenic bacteria.
- R23DE-05036-03 (OBM) CLARK, GLENN T**, UNIVERSITY OF CALIFORNIA, CENTER FOR THE HEALTH SCIENCES, LOS ANGELES, CALIF 90024 Nocturnal masseter muscle activity and jaw dysfunction (human).

PROJECT NO., REVIEW GROUP, INVESTIGATOR, ADDRESS, AND TITLE

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R23DE-05037-03 (OBM) HSIEH, H STEVE, UNIVERSITY OF ALABAMA, UNIVERSITY STATION, BIRMINGHAM, ALA 35294 Biochemical role of zinc in teeth and bones.

R01DE-05041-03 (HED) GOLDMAN, ALLEN S, JOSEPH STOKES, JR RES INST, 34TH STREET & CIVIC CTR BLVD, PHILADELPHIA, PA 19104 Orofacial anomalies in phenotypic teratogenesis (mice, human).

R23DE-05042-03 (OBM) JENSEN, OLIVIND E, EASTMAN DENTAL CENTER, 625 ELMWOOD AVENUE, ROCHESTER, N Y 14620 Assessment of wear of four different sealants in vivo (human).

R01DE-05049-01 (OBM) BOACKLE, ROBERT J, UNIVERSITY OF SOUTH CAROLINA, 171 ASHLEY AVENUE, CHARLESTON, S C 29403 Saliva-complement interactions and oral mucosal defense.

R23DE-05050-02 (OBM) LEVINE, MARTIN, UNIVERSITY OF OKLAHOMA, P O BOX 26901, OKLAHOMA CITY, OKLA 73190 Sources of toxins from human dental plaque.

R01DE-05054-03 (OBM) RANNEY, RICHARD R, VIRGINIA COMMONWEALTH UNIV, 520 NORTH 12TH STREET, RICHMOND, VA 23298 Periodontal diseases--Microbiological studies.

R23DE-05062-03 (OBM) HASTY, DAVID L, UNIVERSITY OF TENNESSEE, 875 MONROE AVENUE, MEMPHIS, TENN 38163 Tissue interactions during odontogenesis.

R23DE-05072-03 (OBM) BOSHELL, JERRY L, MEDICAL COLLEGE OF GEORGIA, 1120 15TH STREET, AUGUSTA, GA 30912 Stimulation of regenerating rat submandibular glands.

R01DE-05078-05 (SSS) ENLOW, DONALD H, CASE WESTERN RESERVE UNIV, 2123 ABINGTON ROAD, CLEVELAND, OHIO 44106 Craniofacial growth and remodeling (human).

R01DE-05089-03 (VR) GENTRY, GLENN A, UNIVERSITY OF MISSISSIPPI, 2500 NORTH STATE STREET, JACKSON, MISS 39216 Oral herpes simplex--An approach to dental therapy (hamsters).

R01DE-05092-03 (OBM) BUTLER, WILLIAM T, UNIVERSITY OF ALABAMA, UNIVERSITY STATION, BIRMINGHAM, ALA 35294 Proteins involved in dentinogenesis.

R01DE-05102-04 (MBC) DOYLE, RONALD J, SCHOOL OF DENTISTRY, P O BOX 35260, LOUISVILLE, KY 40292 Potential anti-caries agents (rats).

R01DE-05104-02 (OBM) BANDT, CARL L, UNIVERSITY OF MINNESOTA, 515 S E DELAWARE, MINNEAPOLIS, MINN 55455 Periodontitis--Microbial etiology and prediction.

R01DE-05109-02 (OBM) SIMMONS, DAVID J, WASHINGTON UNIVERSITY, 4559 SCOTT AVENUE, ST LOUIS, MO 63110 Composite bone grafts in dentistry and medicine.

R01DE-05112-03 (AFY) GANS, CARL, UNIVERSITY OF MICHIGAN, DIVISION OF BIOLOGICAL SCI, ANN ARBOR, MICH 48109 Muscle activity and control in mastication (mammals, lizards).

R23DE-05117-03 (IMB) PLUSKIN, MICHAEL E, UNIVERSITY OF PENNSYLVANIA, 4001 SPRUCE STREET, PHILADELPHIA, PA 19104 Enhancement of oral cancer after allografting (mice).

R01DE-05123-04 (MBC) HOLT, STANLEY C, UNIVERSITY OF MASSACHUSETTS, DEPARTMENT OF MICROBIOLOGY, AMHERST, MASS 01003 Periodontopathogenic bacteria:chemical-biologic nature (mammals).

R01DE-05129-04 (OBM) BOWEN, RAFAEL L, AMERICAN DENTAL ASSN HLTH FDN, 211 EAST CHICAGO AVENUE, CHICAGO, ILL 60611 Improvement of preventive and restorative materials.

P01DE-05130-03 (SSS) BONICA, JOHN J, 1959 N E PACIFIC, SEATTLE, WASH 98195 Dental/orofacial pain--Mechanisms behavior and modulation.

P01DE-05130-03 0006 (SSS) DWORKIN, SAMUEL F, Dental/orofacial pain--Mechanisms behavior and modulation--Acute pain in research and clinical settings.

P01DE-05130-03 0009 (SSS) DONG, WILLIE K, Dental/orofacial pain--Mechanisms behavior and modulation--Dental near and far field potentials and pain reactivity (cats, monkeys).

R01DE-05136-03 (OBM) ROBERTS, W EUGENE, UNIVERSITY OF THE PACIFIC, 2155 WEBSTER STREET, SAN FRANCISCO, CALIF 94115 Osteoclast origin and histogenesis in periodontium (rats).

R01DE-05137-03 (OBM) GWINNETT, A JOHN, S U N Y - AT STONY BROOK, DEPT ORAL BIOLOGY & PATHOLOGY, STONY BROOK, N Y 11794 Microscopic and clinical study of cervical erosion.

R01DE-05138-03 (OBM) TAMARIN, ARNOLD, UNIVERSITY OF WASHINGTON, DEPARTMENT OF ORAL BIOLOGY, SEATTLE, WASH 98195 Visceral arches and oro-facial morphogenesis (mice, monkeys).

P50DE-05139-04 (DSR) RANNEY, RICHARD R, VIRGINIA COMMONWEALTH UNIV, 520 NORTH TWELFTH STREET, RICHMOND, VA 23298.

P50DE-05139-04 0001 (DSR) RANNEY, RICHARD R --Microbiology.

P50DE-05139-04 0002 (DSR) RANNEY, RICHARD R --Immunological investigations.

P50DE-05139-04 0003 (DSR) RANNEY, RICHARD R --Polymorphonuclear leukocyte functions.

R01DE-05141-03 (OBM) KURAMITSU, HOWARD K, NORTHWESTERN UNIVERSITY, 303 EAST CHICAGO AVENUE, CHICAGO, ILL 60611 Cariogenic mechanisms of gingival plaque bacteria.

R23DE-05142-03 (OBM) SHEETZ, JAMES H, JR, UNIVERSITY OF ALABAMA, UNIVERSITY STATION, BIRMINGHAM, ALA 35294 Control mechanisms in salivary gland development (rats).

R01DE-05144-03 (BM) JOHNSON, RUSSELL C, UNIVERSITY OF MINNESOTA, 420 DELAWARE STREET, S E, MINNEAPOLIS, MINN 55455 Periodontal disease--Role of spirochetes (rabbits, human).

R01DE-05145-03 (OBM) MOSS, MELVIN L, COLUMBIA UNIVERSITY, 630 WEST 168TH STREET, NEW YORK, N Y 10032 Adaptive cranial skeletal growth (rats).

R23DE-05155-02 (OBM) HUME, WYATT R, UNIVERSITY OF CALIFORNIA, SCHOOL OF DENTISTRY, LOS ANGELES, CALIF 90024 Active principles of dental pulp therapeutic agents.

R01DE-05156-03 (OBM) CROWLE, ALFRED J, UNIVERSITY OF COLORADO, 4200 EAST NINTH AVENUE, DENVER, COLO 80262 Immunoidentification of periodontal plaque bacteria.

R01DE-05159-03 (OBM) BYERS, MARGARET R, 1959 N E PACIFIC RN-10, SEATTLE, WASH 98195 Distribution and ultrastructure of dental innervation (cats, rats).

R01DE-05165-03 (HED) TYAN, MARVIN L, VETERANS ADMINISTRATION, WILSHIRE & SAWTELLE BLVDs, LOS ANGELES, CALIF 90073 Genetic control of susceptibility to cleft palate (mice).

R01DE-05168-03 (HED) HACKNEY, JOHN F, UNIVERSITY OF SOUTH FLORIDA, 12901 NORTH 30TH STREET, TAMPA, FLA 33612 Glucocorticoid receptors and cleft palate (mice).

R01DE-05180-03 (OBM) DANE0-MOORE, LOLITA, TEMPLE UNIVERSITY, DEPT OF MICROBIOLOGY & IMMUNOL, PHILADELPHIA, PA 19140 Composition of S mutants in different growth environments.

R01DE-05188-03 (OBM) HOCK, JANET M, UNIVERSITY OF CONNECTICUT, DEPARTMENT OF PERIODONTICS, FARMINGTON, CONN 06032 Blood vessel response in periodontal disease (dogs, rats).

R01DE-05190-03 (OBM) MACKENZIE, IAN C, UNIVERSITY OF IOWA, DENTAL SCIENCE BUILDING, IOWA CITY, IOWA 52242 Factors determining variation in adult oral mucosa.

R01DE-05194-03 (EVR) NAHMIA, ANDRE J, 69 BUTLER STREET, S E, ATLANTA, GA 30303 Latency of herpes simplex in oro-facial infections (human).

R01DE-05198-02 (SSS) PROFFIT, WILLIAM R, UNIVERSITY OF NORTH CAROLINA, SCHOOL OF DENTISTRY, CHAPEL HILL, N C 27514 Influences on vertical dento-facial growth (guinea pigs, children, adults).

R01DE-05203-03 (CMS) VIG, PETER S, UNIVERSITY OF NORTH CAROLINA, SCHOOL OF DENTISTRY 209-H, CHAPEL HILL, N C 27514 Speech adaptations to orthognathic surgery (human).

R01DE-05204-03 (BPO) ROSENFELD, JOEL P, NORTHWESTERN UNIVERSITY, 2021 SHERIDAN ROAD, EVANSTON, ILL 60201 Operant neural control in trigeminal pain systems (rat).

R01DE-05208-03 (NEUA) YOUNG, RONALD F, LAC HARBOR-UCLA MED CENTER, 1000 WEST CARSON STREET, TORRANCE, CALIF 90509 Mechanism of dental and facial sensation (monkeys).

R01DE-05209-04 (GMB) COHN, DAVID V, VETERANS ADMIN MEDICAL CENTER, 4801 LINWOOD BOULEVARD, KANSAS CITY, MO 64128 Metabolic pathways in bone.

R01DE-05210-03 (GMB) TOVERUD, SVEIN U, UNIVERSITY OF NORTH CAROLINA, DENTAL RESEARCH CENTER, CHAPEL HILL, N C 27514 Acid phosphatases in developing bones and teeth (rats).

R01DE-05215-03 (OBM) PROFFIT, WILLIAM R, UNIVERSITY OF NORTH CAROLINA, SCHOOL OF DENTISTRY 209-H, CHAPEL HILL, N C 27514 Influences on stability following orthognathic surgery.

R01DE-05218-03 (BM) JOHNSON, JOHN L, VIRGINIA POLYTECHNIC INSTITUTE, ANAEROBE LABORATORY, BLACKSBURG, VA 24061 DNA homologies among bacteria of periodontal diseases.

R01DE-05224-01 (OBM) APOSTOLOPOULOS, A X, UNIVERSITY OF COLORADO, 4200 EAST NINTH AVENUE, DENVER, COLO 80262 Enamel silylation as a caries prevention method (human, animals).

R23DE-05232-03 (OBM) CARLSON, DAVID S, UNIVERSITY OF MICHIGAN, CTR FOR HUMAN GROWTH & DVLPMNT, ANN ARBOR, MICH 48109 Growth and function of the muscles of mastication (monkeys).

R23DE-05240-03 (OBM) HABER, JEROME, TUFTS UNIVERSITY, ONE KNEELAND STREET, BOSTON, MASS 02111 Immunological studies--Caries and periodontal disease (mice).

R01DE-05249-02 (GMB) WATSON, EILEEN L, UNIVERSITY OF WASHINGTON, SCHOOL OF MEDICINE, SEATTLE, WASHINGTON 98195 Salivary secretory role of calcium (mice).

R01DE-05251-02 (SSS) KELLER, PATRICIA J, UNIVERSITY OF WASHINGTON, DEPARTMENT OF ORAL BIOLOGY SB-, SEATTLE, WASH 98195 Salivary gland secretory mechanisms (rats).

R01DE-05252-01 (OBM) FINE, DANIEL H, COLUMBIA UNIVERSITY, 630 WEST 168TH STREET, NEW YORK, N Y 10032 Bidirectional effects of subgingival dental plaque.

R01DE-05255-03 (OBM) SAKAMOTO, SEIZABURO, HARVARD SCHOOL OF DENTAL MED, 188 LONGWOOD AVENUE, BOSTON, MASS 02115 Regulation of collagenase and bone resorption (chick embryos, mice).

R01DE-05271-03 (OBM) SENSEMAN, DAVID M, UNIVERSITY OF PENNSYLVANIA, 4001 SPRUCE STREET/AL, PHILADELPHIA, PA 19104 Neuroeffector transmission in a simple salivary gland (snails, mice).

R01DE-05289-03 (OBM) BAWDEN, JAMES W, UNIVERSITY OF NORTH CAROLINA, DENTAL RESEARCH CENTER, CHAPEL HILL, N C 27514 Fluorine ion binding by early enamel matrix proteins (rats).

R01DE-05292-03 (AFY) KLAUITTER, JEROME J, TULANE UNIVERSITY, MECHANICAL ENGINEERING DEPT, NEW ORLEAN, LA 70118 Biological prosthetic attachment (dog).

R01DE-05305-02 (EDC) MELAMED, BARBARA G, UNIVERSITY OF FLORIDA, BOX J-165, GAINESVILLE, FLA 32611 Behavioral approaches to pain responses in pedodontics (children).

R01DE-05307-03 (OBM) GRABER, THOMAS M, AMERICAN DENTAL ASSOCIATION, 211 EAST CHICAGO AVENUE, CHICAGO, ILL 60611 Orthodontic treatment with removable appliances (human, monkeys).

R23DE-05310-03 (OBM) CLARK, ROBERT W, JR, WASHINGTON STATE UNIVERSITY, DEPT OF ZOOLOGY, PULLMAN, WASH 99164 Neural control of mandibular movement.

R23DE-05314-03 (OBM) VAIDYANATHAN, TRITALA K, NEW YORK UNIVERSITY, 345 EAST 24TH STREET, NEW YORK, N Y 10010 Dental alloy corrosion research.

R23DE-05316-03 (OBM) FREUND, THOMAS S, FAIRLEIGH DICKINSON UNIVERSITY, SCHOOL OF DENTISTRY, HACKENSACK, N J 07601 Salivary calcium binding proteins and oral disease.

R01DE-05321-02 (OBM) GOLDBERG, A JON, UNIVERSITY OF CONNECTICUT, DEPT OF RESTORATIVE DENTISTRY, FARMINGTON, CONN 06032 Titanium alloys in dentistry.

R01DE-05322-01 (GEN) ERICKSON, ROBERT P, 1137 EAST CATHERINE STREET, ANN ARBOR, MICH 48109 Genetic analysis of birth defects involving septa (human, mice).

R01DE-05323-02 (OBM) EISENMANN, DALE R, BOX 6998, CHICAGO, ILL 60680 Calcium transport in developing dental tissues (frogs, rats).

R01DE-05327-03 (OBM) ANBAR, MICHAEL, S U N Y - AT BUFFALO, 118 CARY HALL, BUFFALO, N Y 14214 Polymeric polyphosphonates on dental caries and plaque (rats).

R01DE-05330-02 (OBM) SHILLITOE, EDWARD J, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, CALIF 94143 Herpes virus antibodies in patients with oral cancer.

R23DE-05331-01 (OBM) PATTERS, MARK R, UNIVERSITY OF CONNECTICUT, SCHOOL OF DENTAL MEDICINE, FARMINGTON, CONN 06032 Local host mechanism in periodontal disease (human, monkeys).

** SEE GLOSSARY OF ABBREVIATIONS for explanation of grant and contract number

PROJECT NO., REVIEW GROUP, INVESTIGATOR, ADDRESS, AND TITLE

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- R23DE-05332-03 (OBM) FELDMAN, ROY S.**, HARVARD SCHOOL OF DENTAL MED , 188 LONGWOOD AVENUE, BOSTON, MASS 02115 Bone in vitro-Ultra-structure and autoradiography (mice).
- R01DE-05334-02 (OBM) GOODSON, JO M.**, FORSYTH DENTAL CENTER, 140 FENWAY, BOSTON, MASS 02115 Periodontal therapy by controlled local drug delivery (human).
- R01DE-05351-02 (SSS) LANDIS, WILLIAM J.**, CHILDREN'S HOSPITAL MED CENTER, 300 LONGWOOD AVENUE, BOSTON, MASS 02115 Electron optical examination of mineralized tissues (animals).
- R01DE-05352-03 (OBM) MANSHEIM, BERNARD J.**, UNIVERSITY OF FLORIDA, J HILLIS MILLER HEALTH CTR, GAINESVILLE, FLA 32610 Immunochemical studies in periodontal disease.
- R01DE-05353-04 (OBM) MABIE, CURTIS P.**, NATIONAL BUREAU OF STANDARDS, AMERICAN DENTAL ASSN HLTH FDN, GAITHERSBURG, MD 20760 Dental porcelains improvement with inorganic polymers.
- R01DE-05354-04 (OBM) BROWN, WALTER E.**, AMERICAN DENTAL ASSOC HLTH FND, 211 EAST CHICAGO AVENUE, CHICAGO, ILL 60611 Prevention of dental caries (rats, human).
- R01DE-05359-01 (OBM) RIVIERE, GEORGE R.**, UNIVERSITY OF CALIFORNIA, SCHOOL OF DENTISTRY, LOS ANGELES, CALIF 90024 Regulation of secretory immunity to S mutants (mice).
- R01DE-05367-02 (HED) WATERMAN, ROBERT E.**, UNIVERSITY OF NEW MEXICO, DEPT OF ANATOMY, ALBUQUERQUE, N MEX 87131 Cranio-facial anomalies in the oel mouse.
- R01DE-05369-03 (PHRA) FIELDS, HOWARD L.**, UNIVERSITY OF CALIFORNIA, DEPARTMENT OF NEUROLOGY, SAN FRANCISCO, CALIF 94143 Factors affecting dental postoperative pain.
- R01DE-05371-01 (EDC) PERTSCHUK, MICHAEL J.**, UNIVERSITY OF PENNSYLVANIA, 1157 GATES BUILDING, PHILADELPHIA, PA 19104 Psychosocial evaluation of craniofacial patients.
- R01DE-05375-01 (OBM) BELL, LEONARD C.**, UNIVERSITY OF QUEENSLAND, DEPARTMENT OF AGRICULTURE, ST LUCIA, QUEENSLAND 4067 Surface composition of biological apatites.
- R01DE-05379-01 (OBM) MOFFETT, BENJAMIN C. JR.**, UNIVERSITY OF WASHINGTON, SCHOOL OF DENTISTRY, SEATTLE, WASH 98195 Morphogenesis and maturation of craniofacial sutures (animals).
- R01DE-05381-01 (OBM) SOLBERG, WILLIAM K.**, UNIVERSITY OF CALIFORNIA, SCHOOL OF DENTISTRY, LOS ANGELES, CALIF 90024 Temporomandibular joint changes in young adults.
- R01DE-05390-03 (PHRA) LEVY, RICHARD A.**, UNIVERSITY OF ILLINOIS, 835 S WOLCOTT AVE P O BOX 6998, CHICAGO, ILL 60680 Opiate action on CNS terminals of tooth pulp fibers (animals).
- R23DE-05393-03 (OBM) HARRIS, RICHARD R.**, UNIVERSITY OF IOWA, IOWA CITY, IOWA 52242 Factors association with hyperplasia of oral mucosa.
- R01DE-05395-02 (OBM) MACKENZIE, IAN C.**, UNIVERSITY OF IOWA, ROOM N422A DENTAL SCI BLDG, IOWA CITY, IOWA 52242 Stem cells in oral mucosa.
- R01DE-05396-02 (OBM) NANDA, RAVINDRA.**, UNIVERSITY OF CONNECTICUT, SCHOOL OF DENTAL MEDICINE, FARMINGTON, CONN 06032 Craniofacial adaptations after maxillary osteotomy (monkeys).
- R01DE-05397-01 (OBM) HARVOLD, EGIL P.**, UNIVERSITY OF CALIFORNIA, 3RD AND PARNASSUS, SAN FRANCISCO, CALIF 94143 Craniofacial bone formation and muscle activity (Rhesus monkey).
- R01DE-05404-03 (OBM) DOSTROVSKY, JONATHAN O.**, UNIVERSITY OF TORONTO, DEPARTMENT OF PHYSIOLOGY, TORONTO ONTARIO, CANADA Dental pain-Trigeminal nucleus caudalis (cats).
- R01DE-05410-02 (OBM) BOOKSTEIN, FRED L.**, UNIVERSITY OF MICHIGAN, 1111 EAST CATHERINE STREET, ANN ARBOR, MICH 48109 Orthodontic treatment effects on craniofacial growth (human).
- R01DE-05412-02 (OBM) KOROSTOFF, EDWARD.**, UNIVERSITY OF PENNSYLVANIA, 4001 SPRUCE STREET, PHILADELPHIA, PA 19104 Electric current, bone remodeling and tooth movement (cats).
- R01DE-05413-02 (OBM) TEITELBAUM, STEVEN L.**, JEWISH HOSPITAL, DEPARTMENT OF PATHOLOGY, ST LOUIS, MO 63110 Bone resorption in periodontal disease.
- R01DE-05414-02 (OBM) LALLY, EDWARD T.**, UNIVERSITY OF PENNSYLVANIA, DEPARTMENT OF PATHOLOGY, PHILADELPHIA, PA 19104 The local immune response in periodontal disease (human).
- R23DE-05418-03 (OBM) BRUNSKI, JOHN B.**, RENSSELAER POLYTECHNIC INST, 7040 ENGINEERING CENTER, TROY, N Y 12181 in vivo forces on endosseous dental implants (dogs).
- R01DE-05423-02 (OBM) O'BRIEN, WILLIAM J.**, UNIVERSITY OF MICHIGAN, SCHOOL OF DENTISTRY, ANN ARBOR, MICH 48109 Diffuse reflectance by esthetic dental materials.
- R23DE-05424-03 (OBM) SMITH, CHARLES E.**, MC GILL UNIVERSITY, 3640 UNIVERSITY STREET, MONTREAL, QUEBEC, CANADA Quantitative studies of lysosomes in amelogenesis (rats).
- R01DE-05427-01 (OBM) STAAT, ROBERT H.**, UNIVERSITY OF LOUISVILLE, POST OFFICE BOX 35260, LOUISVILLE, KY 40232 Adherence mechanisms of oral microbes.
- R23DE-05429-03 (OBM) CLARK, WILLIAM B.**, UNIVERSITY OF FLORIDA, COLLEGE OF DENTISTRY, GAINESVILLE, FLA 32610 Adherence of periodontal disease-associated bacteria.
- R01DE-05436-03 (OBM) RYAN, VIVIAN W.**, STEVENS INSTITUTE OF TECHNOLOGY, DEPARTMENT OF PHYSICS/ENGINEER, HOBOKEN, N J 07030 Salivary proteins in bacterial aggregation/adherence.
- R01DE-05440-02 (HED) MELNICK, MICHAEL.**, UNIVERSITY OF SOUTHERN CALIF, LAB FOR DEVELOPMENTAL BIOLOGY, LOS ANGELES, CALIF 90007 H-2 and teratogen-induced craniofacial malformation (mice).
- R01DE-05441-02 (OBM) ANUSAVICE, KENNETH J.**, MEDICAL COLLEGE OF GEORGIA, SCHOOL OF DENTISTRY, AUGUSTA, GA 30912 Optimization of metal-ceramic restoration design.
- R01DE-05449-02 (OBM) SCHUSTER, GEORGE S.**, MEDICAL COLLEGE OF GEORGIA, SCHOOL OF DENTISTRY, AUGUSTA, GA 30912 Transformation of oral mucosa by herpes simplex virus (hamsters).
- R01DE-05459-02 (OBM) HASSELL, THOMAS M.**, UNIVERSITY OF NORTH CAROLINA, DENTAL RESEARCH CENTER, CHAPEL HILL, N C 27514 Phenyltin-Pathogenesis of gingival overgrowth (cats).
- R01DE-05460-02 (OBM) PASK, JOSEPH A.**, UNIVERSITY OF CALIFORNIA, DEPT OF MATERIALS SCI MIN ENGR, BERKELEY, CALIF 94720 Bonding of dental porcelain to non-precious alloys.

- R01DE-05462-01 (OBM) MALAMUD, DANIEL F.**, UNIVERSITY OF PENNSYLVANIA, 4001 SPRUCE STREET, PHILADELPHIA, PA 19104 Saliva mediated aggregation of oral bacteria (human).
- R01DE-05466-03 (TOX) MITOMA, CHOZO.**, SRI INTERNATIONAL, 333 RAVENSWOOD AVENUE, MENLO PARK, CALIF 94025 Biochemical studies of a sweetener, SRI Oxime V (rats, mice, dogs, monkeys).
- R01DE-05467-02 (GMB) LUBEN, RICHARD A.**, UNIVERSITY OF CALIFORNIA, DIV OF BIOMEDICAL SCIENCES, RIVERSIDE, CALIF 92521 Pathogenesis of localized bone destruction.
- R13DE-05468-01 (NSS) BURSTONE, CHARLES J.**, UNIVERSITY OF CONNECTICUT, DEPARTMENT OF ORTHODONTICS, FARMINGTON, CONN 06032 Symposium on orthodontics and bioengineering (Connecticut).
- R01DE-05476-02 (MCHA) GOODMAN, MURRAY.**, UNIV OF CALIFORNIA, SAN DIEGO, LA JOLLA, CALIF 92093 Novel peptide derived sweeteners.
- R01DE-05483-02 (OBM) HOWELL, DAVID S.**, UNIVERSITY OF MIAMI, DEPARTMENT OF MEDICINE, MIAMI, FLA 33101 Characterization of predermal extracellular fluid (rats).
- R01DE-05487-02 (OBM) KLEIN, LEROY.**, UNIVERSITY HOSPITAL, WEARN RESEARCH BLDG, CLEVELAND, OHIO 44106 Kinetics of mineral recycling in teeth and bone.
- R23DE-05491-02 (OBM) REED-MILLER, CHARLENE.**, FLORIDA STATE UNIVERSITY, DEPT OF GEOLOGY, TALLAHASSEE, FLA 32306 Control of biomineralization in two species (snails).
- R01DE-05494-02 (OBM) PABST, MICHAEL J.**, NATL JEWISH HOSP & RES CTR, 3800 EAST COLFAX AVENUE, DENVER, COLO 80206 Activation of macrophages in periodontal disease.
- R01DE-05495-02 (OBM) WISOTZKY, JOEL.**, CASE WESTERN RESERVE UNIV, 2123 ABINGTON ROAD, CLEVELAND, OHIO 44106 Myofibroblast contraction in periodontium (rats).
- R23DE-05497-02 (EDC) REISINE, SUSAN T.**, UNIVERSITY OF CONNECTICUT, DEPARTMENT OF BEHAVIORAL SCI, FARMINGTON, CONN 06032 Dental disease and work loss (human).
- R23DE-05501-02 (BM) HERZBERG, MARK C.**, UNIVERSITY OF MINNESOTA, 515 DELAWARE ST S E, MINNEAPOLIS, MINN 55455 Platelet-Streptococcal interactions in endocarditis (human, rabbits).
- R01DE-05505-02 (OBM) PARK, BYUNG H.**, CHILDREN'S HOSPITAL, 219 BRYANT STREET, BUFFALO, N Y 14222 Periodontitis and host defense in juvenile diabetes (human).
- R23DE-05507-02 (OBM) MOORE, PAUL A.**, HARVARD SCHOOL OF DENTAL MED, 188 LONGWOOD AVENUE, BOSTON, MASS 02115 Psychomotor impairment related to N2O exposure (human).
- R01DE-05510-02 (OBM) CURZON, MARTIN E.**, EASTMAN DENTAL CENTER, 625 ELMWOOD AVENUE, ROCHESTER, N Y 14620 Physico-chemistry of dentium in caries lesions.
- R01DE-05511-02 (EDC) HEFFERREN, JOHN J.**, AMERICAN DENTAL ASSOCIATION, 211 EAST CHICAGO AVENUE, CHICAGO, ILL 60611 Evanston-Oak park fluoridation study after 25 years (human).
- R01DE-05512-02 (OBM) RUTHERFORD, R BRUCE.**, VIRGINIA COMMONWEALTH UNIV, 520 N 12TH STREET, RICHMOND, VA 23298 Role of macrophages in periodontal disease.
- R23DE-05519-02 (OBM) BARAN, GEORGE R.**, TEMPLE UNIVERSITY, DEPT OF OPERATIVE DENTISTRY, PHILADELPHIA, PA 19140 Oxidation behavior of Ni-base crown and bridge alloys.
- R01DE-05525-02 (OBM) SQUIER, CHRISTOPHER A.**, UNIVERSITY OF IOWA, DENTAL SCIENCE BUILDING, IOWA CITY, IOWA 52242 Nature of the permeability barrier in oral epithelium.
- R23DE-05527-02 (EDC) FISCHER, STEVEN C.**, BOSTON UNIVERSITY, 80 EAST CONCORD STREET, BOSTON, MASS 02118 Behavioral treatments for nocturnal bruxism (human).
- R01DE-05530-01 (OBM) WEBER, DENNIS F.**, UNIVERSITY OF ILLINOIS, BOX 6998, CHICAGO, ILL 60680 Internal structure of dentine (human, rats).
- R01DE-05531-03 (OBM) ELLISON, SOLON A.**, COLUMBIA UNIVERSITY, SCH OF DENTAL & ORAL SURGERY, NEW YORK, N Y 10032 Salivary immune factors (human, bacteria).
- R23DE-05540-03 (OBM) BAKKER, VERONICA M.**, FORSYTH DENTAL CENTER, 140 FENWAY, BOSTON, MASS 02115 Condylotomy and anterior positioning of the mandible.
- R01DE-05542-03 (OBM) BAYS, ROBERT A.**, MEDICAL COLLEGE OF GEORGIA, DEPARTMENT OF ORAL SURGERY, AUGUST, GA 30912 Stability of orthognathic surgical procedures (monkeys).
- R01DE-05550-01 (HED) GREENE, ROBERT M.**, JEFFERSON MEDICAL COLLEGE, DEPARTMENT OF ANATOMY, PHILADELPHIA, PA 19107 Cell death during craniofacial embryogenesis.
- R01DE-05555-01 (HED) WATERMAN, ROBERT E.**, UNIVERSITY OF NEW MEXICO, DEPARTMENT OF ANATOMY, ALBUQUERQUE, N MEX 87131 Cell migration in the teleost embryo.
- R01DE-05558-01 (OBM) VARGERVIK, KARIN.**, UNIVERSITY OF CALIFORNIA, 3RD AND PARNASSUS, SAN FRANCISCO, CALIF 94143 Sensory alterations of craniofacial form (Rhesus monkeys).
- R01DE-05560-01 (OBM) SUITER, VERA L.**, VA WADSWORTH MEDICAL CENTER, BUILDING 114, LOS ANGELES, CALIF 90073 Rapid identification of oral bacteria.
- R01DE-05563-02 (OBM) SCHNITMAN, PAUL A.**, HARVARD SCH OF DENTAL MEDICINE, 188 LONGWOOD AVENUE, BOSTON, MASS 02115 The blade implant-Clinical efficacy and safety (human).
- R23DE-05572-02 (EVR) PARK, NO HEE.**, EYE RES INST OF RETINA FDN, 20 STANFORD STREET, BOSTON, MASS 02114 New antiviral therapy for oral and other herpes (mice, guinea pig, rabbits).
- R01DE-05574-01 (OBM) ALLEY, KEITH E.**, CASE WESTERN RESERVE UNIV, 2119 ABINGTON ROAD, CLEVELAND, OHIO 44106 Neural aspects of craniofacial morphogenesis (frogs).
- R01DE-05582-01 (OBM) LEONARD, MYER S.**, UNIVERSITY OF MINNESOTA, DEPT/ ORAL/MAXILLOFACIAL SURG, MINNEAPOLIS, MINN 55455 Computer graphic analysis of cranio-facial morphology.
- R01DE-05586-01 (OBM) GARANT, PHILIAS R.**, S U N Y - AT STONY BROOK, ORAL BIOLOGY & PATHOLOGY DEPT, STONY BROOK, N Y 11794 Cell surface studies of the enamel organ (mice).
- R23DE-05592-02 (OBM) TZORTZATOU, GEORGIA G.**, CHILDRENS HOSPITAL, 34TH STREET & CIVIC CENTER, PHILADELPHIA, PA 19104 Biochemical mechanism of steroid-induced clefting (mice).

** SEE GLOSSARY OF ABBREVIATIONS for explanation of grant and contract number

PROJECT NO., REVIEW GROUP, INVESTIGATOR, ADDRESS, AND TITLE

PROJECT NO., REVIEW GROUP, INVESTIGATOR, ADDRESS, AND TITLE

- R01DE-05596-02 (OBM) RAWLS, HENRY R.**, LOUISIANA STATE UNIVERSITY, SCHOOL OF DENTISTRY, BOX 226, NEW ORLEANS, LA 70119 Topically-applied polymers for caries prevention.
- R23DE-05599-02 (OBM) KORNMAN, KENNETH S.**, UNIVERSITY OF CONNECTICUT, DEPARTMENT OF PERIODONTICS, FARMINGTON, CONN 06032 Microbiology of ligature-induced periodontitis.
- R23DE-05605-01 (OBM) KIM, SYNGCUK**, COLUMBIA UNIVERSITY, 630 W 168 ST, NEW YORK, N Y 10032 The humoral regulation of pulp circulation (rats).
- R01DE-05606-02 (OBM) FIVES-TAYLOR, PAULA M.**, UNIVERSITY OF VERMONT, GIVEN BUILDING, BURLINGTON, VT 05405 Pili of *S. sanguis* and their role in adhesion (human, rabbits).
- R23DE-05607-02 (OBM) KIMMEL, DONALD B.**, UNIVERSITY OF UTAH, BUILDING 522, SALT LAKE CITY, UTAH 84112 Cells of alveolar bone during hyperparathyroidism (rats).
- R01DE-05616-03 (CBY) MEIER, STEPHEN P.**, UNIVERSITY OF TEXAS, DEPARTMENT OF ZOOLOGY, AUSTIN, TEX 78712 Matrix-cell interaction in craniofacial development (chick embryos).
- R01DE-05622-01 (OBM) SADOWSKY, DONALD**, ALBERT EINSTEIN COLL OF MED, BRONX, N Y 10461 Rx for dental patients at risk for endocarditis (dentists).
- R01DE-05626-01 (OBM) SCHENKEIN, HARVEY A.**, MEDICAL COLLEGE OF VIRGINIA, BOX 637 MCY STATION, RICHMOND, VA 23298 Role of complement in periodontal disease.
- R23DE-05627-02 (OBM) CEDERQUIST, K. ROBERT**, CASE WESTERN RESERVE UNIV, 2123 ABLINGTON ROAD, CLEVELAND, OHIO 44106 Effects of mechanical forces on craniofacial growth (monkeys, rabbits).
- R23DE-05628-02 (NTN) CERKLEWSKI, FLORIAN L.**, OREGON STATE UNIVERSITY, DEPT OF FOODS AND NUTRITION, CORVALLIS, OREG 97331 Influence of trace metals on dental health (rats).
- R01DE-05630-01 (CBY) ERICKSON, CAROL A.**, UNIVERSITY OF CALIFORNIA, DEPARTMENT OF ZOOLOGY, DAVIS, CALIF 95616 Matrix/cell surface in neural crest cell morphogenesis (mice, chick, quail).
- R01DE-05632-01 (OBM) CUTLER, LESLIE S.**, UNIVERSITY OF CONNECTICUT, SCHOOL OF DENTAL MEDICINE, FARMINGTON, CONN 06032 Development of salivary gland secretory function (rats).
- R23DE-05633-02 (OBM) YU, JIA-HUEY**, UNIVERSITY OF ALABAMA, DEPT OF PHYSIOLOGY & BIOPHYSICS, BIRMINGHAM, ALA 35294 Modulating role of prostaglandins in salivary gland function (rats).
- R01DE-05634-01 (OBM) HAWLEY, ROBERT J.**, GEORGETOWN UNIVERSITY, DEPARTMENT OF MICROBIOLOGY, WASHINGTON, D C 20007 Antibiotic resistance transfer in oral streptococci (human).
- R01DE-05636-01 (OBM) AVERY, JAMES K.**, UNIVERSITY OF MICHIGAN, 1011 NORTH UNIVERSITY AVENUE, ANN ARBOR, MICH 48109 Cellular mediators in tooth maintenance and repair (rats).
- R01DE-05637-01 (OBM) DRAUGHN, ROBERT A.**, UNIVERSITY OF SOUTH CAROLINA, 171 ASHLEY AVE, CHARLESTON, S C 29403 Mechanical properties of dental composite materials.
- R01DE-05640-01 (OBM) HAMMOND, BENJAMIN F.**, UNIVERSITY OF PENNSYLVANIA, 4001 SPRUCE STREET, PHILADELPHIA, PA 19104 Cytotoxicity of periodontopathic bacteria.
- R01DE-05652-01 (OBM) GERMAINE, GREG R.**, UNIVERSITY OF MINNESOTA, DIVISION OF ORAL BIOLOGY, MINNEAPOLIS, MINN 55455 Biological role of lysozyme in human saliva.
- R01DE-05659-01 (OBM) DELFINO, JOHN J.**, WASHINGTON UNIVERSITY, DEPT-ORAL-MAXILLOFACIAL SURG, ST LOUIS, MO 63110 Surgical and radiographic evaluation of the temporomandibular joint (human).
- R01DE-05666-01 (OBM) SLOMIANY, BRONISLAW L.**, NEW YORK MEDICAL COLLEGE, DEPARTMENT OF MEDICINE, NEW YORK, N Y 10029 Biochemistry of salivary lipids (monkeys, rats, human).
- R01DE-05669-01 (OBM) POTTER, ROSARIO H.**, INDIANA UNIVERSITY, 1121 WEST MICHIGAN STREET, INDIANAPOLIS, IND 46202 Chorion type and dental morphology in twins.
- R01DE-05678-02 (OBM) SIEGEL, IVENS A.**, UNIVERSITY OF ILLINOIS, SCHOOL OF CLINICAL MEDICINE, URBANA, ILL 61801 Salivary changes after cancer chemotherapeutic drugs.
- R01DE-05679-01 (OBM) LASKIN, DANIEL M.**, UNIVERSITY OF ILLINOIS, P O BOX 6998, CHICAGO, ILL 60680 Pathophysiology of MPD and other facial pain syndromes (animals).
- R01DE-05684-01 (OBM) BIXLER, DAVID**, INDIANA UNIVERSITY, 1121 WEST MICHIGAN STREET, INDIANAPOLIS, IND 46202 Saliva proteins-Chemistry, genetics and oral health.
- R01DE-05690-01 (OBM) LEBLOND, CHARLES P.**, MCGILL UNIVERSITY, 3640 UNIVERSITY STREET, MONTREAL, P Q, CANADA H3A 2B2 Localization of the procollagens in dental tissues.
- R01DE-05696-01 (SSS) STINSON, MURRAY W.**, S U N Y - AT BUFFALO, DEPARTMENT OF MICROBIOLOGY, BUFFALO, N Y 14214 Streptococcus mutants interaction with animal tissue (also human).
- R01DE-05698-01 (OBM) PHILLIPS, CEIB L.**, UNIVERSITY OF NORTH CAROLINA, SCHOOL OF DENTISTRY, CHAPEL HILL, N C 27514 Evaluation of orthognathic surgery patients.
- R01DE-05706-01 (OBM) ROBERTSON, PAUL B.**, UNIVERSITY OF CONNECTICUT, 263 FARMINGTON AVENUE, FARMINGTON, CONN 06032 Role of microbial collagenases in periodontal disease.
- R01DE-05722-02 (OBM) ARNOLD, ROLAND R.**, UNIVERSITY OF LOUISVILLE, POST OFFICE BOX 35260, LOUISVILLE, KY 40232 Bactericidal activity of lactoferrin on oral flora.
- R01DE-05723-01 (OBM) LOPATIN, DENNIS E.**, UNIVERSITY OF MICHIGAN, 1011 NORTH UNIVERSITY AVENUE, ANN ARBOR, MICH 48109 Spirochete influence on immunity in oral disease.
- R01DE-05728-01 (OBM) BRADLEY, ROBERT M.**, UNIVERSITY OF MICHIGAN, 1011 NORTH UNIVERSITY AVENUE, ANN ARBOR, MICH 48109 Role of chemoreceptors in craniofacial function (lambs).
- R01DE-05729-01 (OBM) BAKER, JOHN J.**, UNIVERSITY OF PITTSBURGH, 636 SALK HALL, PITTSBURGH, PA 15261 Etiological mechanisms in periodontal disease.
- R01DE-05732-02 (OBM) REED, MICHAEL J.**, UNIVERSITY OF MISSISSIPPI, 2500 NORTH STATE STREET, JACKSON, MISS 39216 Specificity of cell mediated immune response in periodontal disease.
- R23DE-05735-01 (HED) BURK, DOROTHY T.**, UNIVERSITY OF THE PACIFIC, 2155 WEBSTER STREET, SAN FRANCISCO, CALIF 94115 Role of hyaluronate in primary palate morphogenesis (mice embryos).

- R01DE-05738-01 (OBM) CROMPTON, ALFRED W.**, HARVARD UNIVERSITY, MUSEUM OF COMPARATIVE ZOOLOGY, CAMBRIDGE, MASS 02138 Mastication, food transport, and swallowing in primates.
- R01DE-05744-01 (OBM) KIYAK, H. ASUMAN**, UNIVERSITY OF WASHINGTON, DEPT OF COMMUNITY DENTISTRY, SEATTLE, WASH 98195 Psychosocial factors in orthognathic surgery (human).
- R01DE-05747-01 (OBM) STASHENKO, PHILIP**, FORSYTH DENTAL CENTER, 140 FENWAY, BOSTON, MASS 02115 Monoclonal antibody analysis of *S. mutans* antigens.
- R23DE-05749-01 (OBM) KOUSVELARI, ELENI E.**, UNIVERSITY OF CONNECTICUT, SCHOOL OF DENTAL MEDICINE, FARMINGTON, CONN 06032 Salivary proline-rich proteins-Localization/secretion (monkeys).
- R13DE-05752-01 (NSS) VEIS, ARTHUR**, NORTHWESTERN UNIVERSITY, 303 E CHICAGO AVENUE, CHICAGO, ILL 60611 Conference on biology of mineralized connective tissues.
- R13DE-05753-01 (NSS) GENCO, ROBERT J.**, S U N Y AT BUFFALO, 4510 MAIN STREET, BUFFALO, N Y 14226 Symposium on host-bacteria in periodontal diseases.
- R01DE-05758-01 (OBM) BIXLER, DAVID**, INDIANA UNIVERSITY, 1121 WEST MICHIGAN STREET, INDIANAPOLIS, IND 46202 Genetic linkage study of cleft lip-palate in Denmark.
- R01DE-05761-02 (OBM) STANFORD, JOHN W.**, AMERICAN DENTAL ASSN HLTH FDN, 211 EAST CHICAGO AVENUE, CHICAGO, ILL 60611 Improved dental instruments and materials.
- R01DE-05764-02 (PHRA) PUTNEY, JAMES W., JR.**, MED COLL OF VIRGINIA, V C U, DEPARTMENT OF PHARMACOLOGY, RICHMOND, VA 23298 Cellular pharmacology of salivary secretion (rats).
- R01DE-05769-03 (OBM) REITH, EDWARD J.**, TEMPLE UNIV SCH OF DENTISTRY, 3223 NORTH BROAD STREET, PHILADELPHIA, PA 19140 Ultrastructure of tooth development.
- R01DE-05771-01 (OBM) POTTER, ROSARIO H.**, INDIANA UNIVERSITY SCH OF DENT, 1121 WEST MICHIGAN STREET, INDIANAPOLIS, IND 46202 Quantitative dental traits in man-Major gene effects.
- R01DE-05773-01 (OBM) SIMPSON, WAITS A.**, VETERANS ADMIN MEDICAL CENTER, 1030 JEFFERSON AVENUE, MEMPHIS, TENN 38104 Ligand receptor interactions of cariogenic bacteria.
- R23DE-05777-01 (OBM) STUCHELL, ROBERT N.**, COLUMBIA UNIVERSITY, 630 WEST 168TH STREET, NEW YORK, N Y 10032 Cationic protein in sub-mandibular saliva (goats, rabbits, human).
- R23DE-05789-01 (EI) GOLDSTINE, STEVEN N.**, CASE WESTERN RESERVE UNIV, 2123 ABLINGTON ROAD, CLEVELAND, OHIO 44106 IgA receptor bearing oral cells in cystic fibrosis (human).
- R23DE-05793-01 (PBC) UUITO, VELI-JUKKA V.**, NORTHWESTERN UNIV MEDICAL SCH, 303 E CHICAGO AVENUE, CHICAGO, ILL 60611 Degradation of collagen in inflammation (human gingiva).
- R23DE-05799-01 (OBM) INGERSOLL, BARBARA D.**, WEST VIRGINIA UNIVERSITY, DEPT OF BEHAVIORAL MEDICINE, MORGANTOWN, W VA 26506 Behavioral methods for pedodontic management (human).
- R01DE-05800-01 (OBM) DE VORE, DALE P.**, UNIVERSITY OF MINNESOTA, 18-228 HEALTH SCIENCES UNIT A, MINNEAPOLIS, MINN 55455 Formation and biochemical composition of sea mussel.
- R23DE-05809-01 (OBM) EISENBERG, ARTHUR D.**, EASTMAN DENTAL CENTER, 625 ELMWOOD AVENUE, ROCHESTER, N Y 14620 Effects of fluoride on physiology of oral bacteria.
- R01DE-05817-01 (OBM) BIRKEDAL-HANSEN, HENNING**, UNIVERSITY OF ALABAMA, SCHOOL OF DENTISTRY, BIRMINGHAM, ALA 35294 Gingival collagenase-Quantitation and localization (rabbits, mice, human).
- R01DE-05832-01 (OBM) DOM, RICHARD M.**, MED UNIVERSITY OF S C, 171 ASHLEY AVENUE, CHARLESTON, S C 29403 Organization of the trigeminal mesencephalic nucleus (monkeys, opossums).
- P01DE-05837-01 (SSS) MORRIS, HUGHLETT L.**, UNIVERSITY OF IOWA, DEPARTMENT OF OTOLARYNGOLOGY, IOWA CITY, IOWA 52242 Growth, surgical, and speech aspects of cleft palate.
- P01DE-05837-01 0001 (SSS) NEXT.** Growth, surgical, and speech aspects of cleft palate-Speech pathology (human).
- P01DE-05837-01 0002 (SSS) MORRIS, HUGHLETT L.** Growth, surgical, and speech aspects of cleft palate-Maxillofacial growth (dogs, tamarins).
- P01DE-05837-01 0003 (SSS) MORRIS, HUGHLETT L.** Growth, surgical, and speech aspects of cleft palate-Speech physiology and anatomy (children, adults).
- P01DE-05837-01 0004 (SSS) MORRIS, HUGHLETT L.** Growth, surgical, and speech aspects of cleft palate-Surgery (human, animals).
- R01DE-05838-02 (CBY) TOOLE, BRYAN P.**, 136 HARRISON AVENUE, BOSTON, MASS 02111 Morphogenetic role of glycosaminoglycans (chick embryo).
- R23DE-05858-01 (OBM) FILEWICH, ROBERT J.**, TEMPLE UNIVERSITY, 3223 N BROAD ST, PHILADELPHIA, PA 19140 Dentists' behavior and treatment outcomes.
- R01DE-05868-01 (OBM) KROGMAN, WILTON M.**, H K COOPER CLINIC, 24 NORTH LIME ST, LANCASTER, PA 17602 Multivariate analysis of craniofacial growth in clefting.
- R23DE-05883-01 (OBM) TURLEY, PATRICK K.**, UNIVERSITY OF CALIFORNIA, SCHOOL OF DENTISTRY, LOS ANGELES, CALIF 90024 Implants as anchors to move teeth and facial bones (dogs, monkeys).
- R23DE-05886-01 (OBM) BAYNE, STEPHEN C.**, UMC SCHOOL OF DENTISTRY, 2500 NORTH STATE STREET, JACKSON, MISS 39216 Organic oligomers for new hydrophobic dental cements.
- R23DE-05887-01 (OBM) KAMEN, PAUL R.**, 630 WEST 168TH STREET, NEW YORK, N Y 10032 Effects of oral bacteria on epithelium in vitro.
- R13DE-05897-01 (OBM) HILDEMAN, WILLIAM H.**, UNIVERSITY OF CALIFORNIA, SCHOOL OF DENTISTRY, LOS ANGELES, CALIF 90024 Oral immunogenetics and tissue transplantation (symposium).
- R13DE-05898-01 (NSS) KATZ, J. LAWRENCE**, RENSSELAER POLYTECHNIC INST, CTR FOR BIOMEDICAL ENGINEERING, TROY, N Y 12181 13th Annual International Biomaterials Symposium - 1981.
- R01DE-05904-01 (BLR) BAUME, LOUIS J.**, UNIVERSITY OF GENEVA, 19, RUE BARTHELEMY-MENN, GENEVA 4, SWITZERLAND Revision of the F.O.I dental lexicon.
- R01DE-05937-01 (GMB) BOYAN-SALYERS, BARBARA D.**, UNIVERSITY OF TEXAS, 7703 FLOYD CURT DRIVE, SAN ANTONIO, TEX 78284 Proteolipids and mineralization of bones and teeth (bacteria, rabbits).

PROJECT IDENTIFICATION DATA

8

PROJECT NO., REVIEW GROUP, INVESTIGATOR, ADDRESS, AND TITLE

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R23DE-05942-01 (OBM) LONG, ROSS E. JR., H K COOPER CLINIC, 24 NORTH LIME STREET, LANCASTER, PA 17602 Airway factors in cleft palate dentofacial deformity.

R23DE-05945-01 (OBM) STUPP, SAMUEL I., UNIVERSITY OF ILLINOIS, DEPT OF CERAMIC ENGINEERING, URBANA, ILL 61801 Physicochemical modifications of dental restoratives.

R23DE-05951-01 (OBM) MANDELL, ROBERT L., VIRGINIA COMMONWEALTH UNIV, BOX 566, MCY STATION, RICHMOND, VA 23298 Selective microbial ecology of periodontosis siblings.

R23DE-05956-01 (PBC) WAITE, JOHN H., UNIVERSITY OF CONNECTICUT, DEPT OF SURGERY, FARMINGTON, CONN 06032 The adhesive of *Mytilus edulis*.

R23DE-05967-01 (OBM) OFFENBACHER, STEVEN., EMORY UNIVERSITY, 1462 CLIFTON ROAD, N E, ATLANTA, GA 30322 Role of prostaglandin E in periodontal disease activity.

R13DE-05982-01 (NSS) BONICA, JOHN J., UNIVERSITY OF WASHINGTON, DEPT OF ANESTHESIOLOGY, SEATTLE, WASH 98195 Third World Congress on Pain (Scotland).

R23DE-05985-01 (OBM) WATSON, ANN Y., HARVARD MEDICAL SCHOOL, 25 SHATTUCK STREET, BOSTON, MASS 02115 Growth factors in salivary secretions.

R01DE-05991-01 (OBM) BIRDSSELL, DALE C., UNIVERSITY OF WASHINGTON, DEPT OF ORAL BIOLOGY HSB SB-22, SEATTLE, WASH 98195 Mechanisms of virulence of oral periodontopathogens.

R01DE-05996-01 (OBM) MARKS, SANDY C. JR., UNIVERSITY OF MASSACHUSETTS, 55 LAKE AVENUE NORTH, WORCESTER, MASS 01605 Alveolar bone metabolism during tooth eruption (Dogs).

R01DE-05999-01 (NTN) ALVARES, OLAV F., UNIVERSITY OF TEXAS, 7703 FLOYD CURL DRIVE, SAN ANTONIO, TEXAS 78284 The role of nutrition in oral health.

R01DE-06000-01 (OBM) JOHNSON, DORTHEA A., UNIVERSITY OF TEXAS, 7703 FLOYD CURL DRIVE, SAN ANTONIO, TEX 78284 Effect of parotid function on saliva and cells.

R01DE-06065-01 (GMB) SCHNEIDER, GARY B., LOYOLA UNIVERSITY, 2160 SOUTH FIRST AVENUE, MAYWOOD, ILL 60153 The role of lymphoid cells in alveolar bone resorption.

R01DE-06070-01 (OBM) WALKER, CLAY B., UNIVERSITY OF FLORIDA, DEPT OF BASIC DENTAL SCIENCES, GAINESVILLE, FLA 32610 Antibiotic susceptibilities of periodontal bacteria.

R01DE-06112-01 (OBM) MERTZ-FAIRHURST, EVA J., MEDICAL COLLEGE OF GEORGIA, 1120 FIFTEENTH STREET, AUGUSTA, GA 30912 Filled sealant as a conservative restorative material (human).

R01DE-06113-01 (OBM) WHITFORD, GARY M., MEDICAL COLLEGE OF GEORGIA, DEPT OF ORAL BIOLOGY, AUGUSTA, GA 30912 Determinants of fluoride in the oral environment (Dogs, rats).

N01DE-12430-00 () DALGARD, DANIEL W.**, VIENNA, VIRGINIA Investigation of anticaries vaccine in primates.

N01DE-12431-00 () MELLBERG, JAMES R.**, ALBANY, NEW YORK Clinical trial of a combined MFP-NaF dentifrice.

N01DE-12432-00 () MELLBERG, JAMES R.**, PISCATAWAY, NEW JERSEY Caries and enamel fluoride.

N01DE-12433-00 () BANDT, CARL**, ST PAUL, MINNESOTA Phase contrast evaluation of subgingival plaque (human).

N01DE-12434-00 () NOT AVAILABLE**, ROCHESTER, NEW YORK Identify cariogenic elements of food.

N01DE-42434-21 () BOYD, DALE D.**, VIENNA, VIRGINIA Anti-caries immunization in sub-human primates.

N01DE-52452-12 () MC CLURE, HAROLD M.**, ATLANTA, GEORGIA Oral facial malformations in the rhesus monkey.

N01DE-62491-12 () SHIOTA, TETSUO**, BIRMINGHAM, ALABAMA Use of mutants of cariogenic streptococci to prevent dental caries (rats).

N01DE-72407-07 () LEVERETT, DENNIS H.**, ROCHESTER, NEW YORK Effect of tooth-cleaning on sodium fluoride rinse.

N01DE-72408-06 () KLEIN, DAVID L.**, ALBANY, NEW YORK Cross-reacting antigens/oral flora acidogenic bacteria.

N01DE-72409-08 () CURZON, MARTIN E.**, ROCHESTER, NEW YORK Effect of strontium, lithium and fluorine on dental plaque (rats, human).

N01DE-82413-05 () POLSON, ALAN M.**, ROCHESTER, NEW YORK Long-term effect of orthodontic treatment.

N01DE-82417-03 () LEVERETT, DENNIS H.**, ROCHESTER, NEW YORK Effect of daily mouthrinsing with fluorides.

N01DE-92418-05 () GHERNA, ROBERT L.**, ROCKVILLE, MARYLAND Characterize and identify pleomorphic oral bacteria.

N01DE-92419-02 () RIPA, LOUIS W.**, STONY BROOK, NEW YORK Efficacy of prior toothcleaning on fluoride treatment.

N01DE-92421-14 () MC KENNA, THOMAS W.**, ROCKVILLE, MARYLAND National caries prevalence survey.

N01DE-92422-04 () ELLISON, SOLON A.**, NEW YORK, NEW YORK Dental plaque and saliva from gastric intubated patients.

** SEE GLOSSARY OF ABBREVIATIONS for explanation of grant and contract number

S U B J E C T I N D E X

ABRASION OF DENTAL MATERIALS

SEE DENTAL MATERIALS, WEAR

ABSCSS, DENTAL

SEE DENTAL ABSCESS

ABSORPTION

SEE BIOLOGICAL TRANSPORT, MEMBRANE PERMEABILITY AND TRANSPORT

ABSORPTION OF DIETARY NUTRIENTS

SEE GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT, DIETARY NUTRIENTS

ABSORPTION OF DRUGS

SEE GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT, DRUGS

ACCEPTANCE OF THERAPY

SEE THERAPY COMPLIANCE

ACETYLCHOLINE

SEE CHOLINE, ACETYLCHOLINE

N-ACETYLMURAMIDE GLUCANOHYDROLASE

SEE CARBOHYDRASES, LYSOZYME

ACETYLSALICYLATES

SEE PHENYLCARBOXYLATES, SALICYLATES, ACETYL-

ACHALASIA (PELVIRECTAL)

SEE CONGENITAL ABNORMALITIES, GASTROINTESTINAL, MEGACOLON CONGENITAL

ACID-AMMONIA LIGASES, L-

GLUTAMATE:AMMONIA LIGASE (ADP)

P50DE-02668-15 0152 Regional dental research center -
Primary structure of proteins in hemostasis and oral biology**ACID-BASE BALANCE**

SEE BODY FLUID BALANCE, ACID-BASE

ACID PHOSPHATASE

SEE PHOSPHOMONESTERASES, ACID PHOSPHATASE

ACIDITY OF URINE

SEE URINE ACIDITY

ACIDS

SEE ACIDS-BASES, ACIDS (GENERAL)

ACIDS-BASES, ACIDS (GENERAL)

SEE ALSO PHOSPHATES

SEE ALSO PHOSPHONATES

SEE ALSO SULFENIC ACIDS

P50DE-02670-15 0014 Institute of Dental Research -

Mechanism of production of carious lesions

P50DE-02731-15 0037 Development support for dental
research institute - Luminescence and polarized light in the
diagnosis and treatment of cariesR01DE-05137-03 Microscopic and clinical study of cervical
erosion**ACIDS-BASES, HYDROGEN-ION****CONCENTRATION**

SEE ALSO BODY FLUID BALANCE, ACID-BASE

R01DE-01830-19 Quantitation of enamel demineralization
mechanismsR01DE-03993-07 Effect of saliva on the metabolism of dental
plaqueR01DE-04926-04 Bacterial coaggregation mechanisms in
dental plaqueR23DE-05316-03 Salivary calcium binding proteins and oral
diseaseR01DE-05495-02 Myofibroblast contraction in periodontium
(rats)R23DE-05809-01 Effects of fluoride on physiology of oral
bacteriaR01DE-06113-01 Determinants of fluoride in the oral
environment (Dogs, rats)**ACOUSTIC NERVE**

SEE NERVOUS SYSTEM, CRANIAL NERVES, ACOUSTIC NERVE

ACROCEPHALOSYNDACTYLIASEE CONGENITAL ABNORMALITIES, SKELETAL,
ACROCEPHALOSYNDACTYLIA**ACROSPHENOSYNDACTYLIA**SEE CONGENITAL ABNORMALITIES, SKELETAL,
ACROCEPHALOSYNDACTYLIA**ACRYLIC POLYMERS (RESINS)**

SEE PLASTICS, ACRYLIC POLYMERS

ACTH

SEE PITUITARY-DIENCEPHALON HORMONES, ACTH

ACTINOMYCES

SEE BACTERIA, ACTINOMYCETALES, ACTINOMYCES*

ACTINOMYCETACEAE

SEE BACTERIA, ACTINOMYCETALES, ACTINOMYCES*

ACTINOMYCETALES

SEE BACTERIA, ACTINOMYCETALES*

ACTINOMYCETALES INFECTIONS

SEE BACTERIAL DISEASES, ACTINOMYCETALES INFECTIONS

ACTINOMYCETES AND RELATED ORGANISMS

SEE BACTERIA, ACTINOMYCETALES*

ACTINOMYCIN

SEE ANTIBIOTICS, ACTINOMYCIN D

ACTINOMYCOSIS

SEE BACTERIAL DISEASES, ACTINOMYCETALES INFECTIONS

ACTION POTENTIALS

SEE ELECTROPOTENTIALS, ACTION POTENTIALS

ACTIVATION OF LYMPHOCYTESSEE IMMUNITY, CELLULAR, LYMPHOCYTE ACTIVATION,
TRANSFORMATION AND PROLIFERATION**ACTIVE IMMUNIZATION**

SEE IMMUNITY, IMMUNIZATION ACTIVE

ACTIVE TRANSPORT

SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT

ACUPUNCTURE

SEE THERAPY, ACUPUNCTURE

ACUPUNCTURE ANALGESIA

SEE THERAPY, ACUPUNCTURE

ACUTE DISEASES (DISORDERS)

SEE DISEASES, ACUTE (GENERAL)

ACUTE TREATMENT, DRUGSSEE DOSAGE AND ROUTE, RATE AND DURATION OF
ADMINISTRATION**ADAPTATION, EMOTIONAL**

SEE PSYCHOLOGICAL ADAPTATION, EMOTIONAL ADJUSTMENT

ADAPTATION, SOCIAL

SEE PSYCHOLOGY SOCIAL, SOCIAL ADJUSTMENT

ADENINE ARABINOSIDESEE PURINE NUCLEOSIDES, ADENINE NUCLEOSIDES, ADENINE
ARABINOSIDE**ADENOCARCINOMA**

SEE NEOPLASMS, ADENOCARCINOMA

ADENOSINE KINASE

SEE PHOSPHOTRANSFERASES, ADENOSINE KINASE

ADENOSINE MONOPHOSPHATE CYCLICSEE PURINE NUCLEOTIDES, ADENINE NUCLEOTIDES, AMP
CYCLIC**ADENOSINE TRIPHOSPHATASE**

SEE PHOSPHATASES, ADENOSINE TRIPHOSPHATASE

ADENOSINE TRIPHOSPHATE

SEE PURINE NUCLEOTIDES, ADENINE NUCLEOTIDES, ATP

ADENYLATE CYCLASE

SEE NUCLEOTIDYL-CYCLEASES, ADENYLATE CYCLASE

ADENYLOSUCCINASE

SEE AMIDINE-LYASES, ADENYLOSUCCINATE LYASE

ADENYLOSUCCINATE LYASE

SEE AMIDINE-LYASES, ADENYLOSUCCINATE LYASE

ADENYLOSUCCINATE SYNTHETASESEE CARBON-NITROGEN LIGASES, IMP:L-ASPARTATE LIGASE
(GDP)**ADHESION**

SEE PHYSICAL PROPERTIES, ADHESION

ADHESIVES

SEE CONSUMER PRODUCTS, GLUES AND ADHESIVES

SEE DENTAL MATERIALS, DENTAL ADHESIVES AND SEALANTS

ADJUSTMENT, EMOTIONAL

SEE PSYCHOLOGICAL ADAPTATION, EMOTIONAL ADJUSTMENT

ADJUSTMENT, SOCIAL

SEE PSYCHOLOGY SOCIAL, SOCIAL ADJUSTMENT

ADOLESCENCE

SEE CHILDREN, ADOLESCENCE (12 TO 21 YRS)

ADRENAL CORTEX HORMONESR01DE-04622-05 Craniofacial anomalies and protein receptors
(mice, human)R01DE-05008-03 Basis of drug induced cleft palate (rats,
mice)R23DE-05582-02 Biochemical mechanism of steroid-induced
clefting (mice)**ADRENAL CORTEX HORMONES, CORTISONE**P50DE-02668-15 0172 Regional dental research center -
Genetic and environmental factors interaction in development
of cleft lip (mice)R01DE-02774-13 Tissue interaction in palatal shelf closure
(mice)** R01DE-05008-03 Basis of drug induced cleft palate (rats,
mice)R01DE-05165-03 Genetic control of susceptibility to cleft
palate (mice)**ADRENAL CORTEX HORMONES, 11-DEOXY-17-****HYDROXYCORTICOSTERONE**R01DE-04622-05 Craniofacial anomalies and protein receptors
(mice, human)**ADRENAL CORTEX HORMONES,****GLUCOCORTICIDS**** R01DE-05168-03 Glucocorticoid receptors and cleft palate
(mice)R01DE-05322-01 Genetic analysis of birth defects involving
septa (human, mice)R23DE-05592-02 Biochemical mechanism of steroid-induced
clefting (mice)**ADRENAL CORTEX HORMONES,
HYDROCORTISONE**R01DE-04622-05 Craniofacial anomalies and protein receptors
(mice, human)**ADRENAL CORTEX HORMONES ANALOGS,
TRIAMCINOLONE**R01DE-05440-02 H-2 and teratogen-induced craniofacial
malformation (mice)**ADRENAL CORTEX HORMONES ANALOGS,
TRIAMCINOLONE ACETONIDE**R01DE-05168-03 Glucocorticoid receptors and cleft palate
(mice)**ADRENAL CORTEX (HORMONES) INHIBITORS**R01DE-05168-03 Glucocorticoid receptors and cleft palate
(mice)**ADRENALINE**

SEE PHENYLALKYLAMINES, CATECHOLAMINES, EPINEPHRINE

ADRENERGIC AGENTS

SEE NEUROPHARMACOLOGICAL AGENTS, SYMPATHOMIMETIC

ADRENERGIC BLOCKING AGENTS

SEE NEUROPHARMACOLOGICAL AGENTS, SYMPATHOLYTIC

ADRENERGIC RECEPTORSSEE NEUROTRANSMITTERS RECEPTORS, ADRENERGIC
RECEPTORS**ADRENERGIC ALPHA RECEPTORS**SEE NEUROTRANSMITTERS RECEPTORS, ADRENERGIC
RECEPTORS, ALPHA RECEPTORS**ADRENERGIC BETA RECEPTORS**SEE NEUROTRANSMITTERS RECEPTORS, ADRENERGIC
RECEPTORS, BETA RECEPTORS**ADRENOCORTICOTROPIC HORMONE**

SEE PITUITARY-DIENCEPHALON HORMONES, ACTH

ADRIAMYCIN

SEE ANTIBIOTICS, ANTHRACYCLINES, ADRIAMYCIN

ADRIBLASTINA

SEE ANTIBIOTICS, ANTHRACYCLINES, ADRIAMYCIN

ADULT ANIMAL

SEE AGE (ANIMAL), MATURE (ADULT)

ADULTS

SEE AGE (HUMAN), ADULT

AEGUORIN

SEE PROTEINS, CALCIUM BINDING PROTEINS

AFFERENT NERVES

SEE NERVOUS SYSTEM, AFFERENT NERVES

AFRO AMERICANS

SEE SOCIAL GROUPS, ETHNIC, AMERICANS, BLACK AMERICANS

AG

SEE METALS, HEAVY METALS, SILVER (COMPOUNDS)

**AGAMMAGLOBULINEMIA AS IMMUNE
DEFICIENCY DISORDER**SEE IMMUNOPATHOLOGY, IMMUNOLOGIC DEFICIENCY
DISORDERS**AGB LOCUS (RATS)**SEE IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX
(LOCUS)**AGE (ANIMAL)**P01DE-01697-19 0040 A research program in craniofacial
problems - Pattern recognition for reconstruction of nasal
capsular anatomyP50DE-02600-15 0028 Support for oral biology research
center - Repletion and coupling in bone volume regulation
(rat)R01DE-03987-07 Gingival collagen metabolism in health and
disease (human, rats)R01DE-04227-07 Adaptations to changes in masticatory
muscle length (monkeys)R01DE-05024-03 Craniofacial abnormalities in mice with
vitamine D resistant ricketsR01DE-05632-01 Development of salivary gland secretory
function (rats)**AGE (ANIMAL), INFANTS**R01DE-04615-04 Fluoride-cadmium interaction in dental caries
(rats, human)P01DE-05837-01 0004 Growth, surgical, and speech aspects
of cleft palate - Surgery (human, animals)**AGE (ANIMAL), INFANTS NEWBORN**

R01DE-02110-17 Salivary gland structure and function (rats)

R01DE-03420-09 Immune phenomena in experimental
periodontal disease (rats)R01DE-03619-09 Biochemistry of tooth eruption, movement
and resorption (cats)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

AGE (ANIMAL), MATURE (ADULT)

- R01DE-05379-01 Morphogenesis and maturation of craniofacial sutures (animals)

AGE (HUMAN)

SEE ALSO AGE (ANIMAL)
SEE ALSO CHILDREN
SEE ALSO EMBRYOLOGY
SEE ALSO PREGNANCY, EMBRYO-FETUS

- P50DE-02731-15 0021 Development support for dental research institute - Bacterial specificity in periodontal disease
P01DE-02847-13 0021 Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)
P01DE-02872-12 0036 Craniofacial dysmorphology - Natural history of cleft lip and palate-Malocclusion
P01DE-02872-12 0061 Craniofacial dysmorphology - Craniofacial dysmorphology
P01DE-02872-12 0062 Craniofacial dysmorphology - Congenital palatopharyngeal incompetence
R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
P01DE-03568-07 0008 Craniofacial anomalies-Etiology and treatment - Craniofacial growth
P01DE-03610-15 0017 Cranio-facial growth and development - Craniofacial profile patterns in normal and malformed prenatals and postnates
R01DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)
R01DE-05104-02 Periodontitis-Microbial etiology and prediction
R01DE-05410-02 Orthodontic treatment effects on craniofacial growth (human)
R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
R01DE-05698-01 Evaluation of orthognathic surgery patients
R01DE-05868-01 Multivariate analysis of craniofacial growth in clefting
R23DE-05942-01 Airway factors in cleft palate dentofacial deformity

AGE (HUMAN), ADULT

SEE ALSO AGING

- ** P01DE-01850-18 0071 Nutritional sources and metabolic roles of fluoride - Fluoride content of infant, toddler and adult foods
R01DE-04047-05 Extensibility characteristics of human cheek
R01DE-05104-02 Periodontitis-Microbial etiology and prediction

AGE (HUMAN), ADULT, MIDDLE AGE (45 TO 64 YRS)

- R01DE-05563-02 The blade implant-Clinical efficacy and safety (human)

AGE (HUMAN), ADULT, OLD AGE (65 TO 99 YRS)

- R01DE-05531-03 Salivary immune factors (human, bacteria)

AGE (HUMAN), ADULT, YOUNG (21 TO 44 YRS)

- P01DE-02847-13 0023 Microbial ecology and its relation to dental disease - Microbiota associated with periodontal diseases (human, rats, hamsters)
** R01DE-05381-01 Temporomandibular joint changes in young adults
R01DE-05531-03 Salivary immune factors (human, bacteria)
R01DE-05563-02 The blade implant-Clinical efficacy and safety (human)

AGE (HUMAN), CHILDREN

SEE CHILDREN

AGGLUTINATION REACTION (AGGLUTININ)

SEE IMMUNOLOGICAL TESTS AND IMMUNOASSAY
AGGLUTINATION REACTION (AGGLUTININ)*

AGGLUTININS

SEE IMMUNOLOGY, ANTIBODIES, AGGLUTININS

AGGLUTININS, PLANT

SEE PLANTS PROTEINS, LECTINS

AGGREGATION, CELLULAR

SEE CELL-CELL INTERACTION, CELL AGGREGATION

AGGRESSIVE OUTREACH

SEE HEALTH CARE SERVICES, CASE FINDING AND OUTREACH

AGING

- ** P01DE-01850-18 0081 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on strain N mice
P50DE-02668-15 0125 Regional dental research center - Collagen crosslinks and the fate of extracellular matrix
P50DE-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues
R01DE-04136-07 Maxillofacial materials-Color study
R01DE-04990-03 Normal and abnormal faces (human)
R01DE-05078-05 Craniofacial growth and remodeling (human)
R01DE-05351-02 Electron optical examination of mineralized tissues (animals)
R01DE-05531-03 Salivary immune factors (human, bacteria)

AIR CONDITIONING, HEATING, VENTILATION

SEE ENVIRONMENT CONTROLLED

AL

SEE METALS, ALUMINUM (COMPOUNDS)

ALBERS-SCHOENBERG DISEASE

SEE METABOLIC DISORDERS INBORN, DYSTOPEPTRODISIS

ALBUMINOIDS, COLLAGEN

- ** R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
** P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)
P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
P50DE-02600-15 0028 Support for oral biology research center - Repletion and coupling in bone volume regulation (rat)
** P50DE-02623-14 0026 Center for oral health research - Collagen biosynthesis in the periodontium
P50DE-02623-14 0027 Center for oral health research - Collagenase in the periodontium
** P50DE-02668-15 0125 Regional dental research center - Collagen crosslinks and the fate of extracellular matrix
P50DE-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology
** P50DE-02668-15 0176 Regional dental research center - Collagen biochemistry and the myeloblastosis associated virus infected cells
P50DE-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues
** P50DE-02670-15 0019 Institute of Dental Research - Chemistry and molecular biology of the connective tissue protein, collagen
** P50DE-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues
P50DE-02731-15 0032 Development support for dental research institute - Epithelial cell basal lamina biosynthesis (rats)
R01DE-03223-11 Kinetics of mineralization of teeth (human)
R01DE-03301-11 Connective tissue of the periodontium-Collagen maturation
** R01DE-03318-10 The molecular nature of gingival and mucosal collagen (rat)
R01DE-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)
R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)
** R01DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)
R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)
R01DE-04125-06 Gingival matrix proteins and periodontal disease (human, mammals)
R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)
R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine
R23DE-05062-03 Tissue interactions during odontogenesis
R01DE-05092-03 Proteins involved in dentinogenesis
R23DE-05332-03 Bone in vitro-Ultrastructure and autoradiography (mice)
R01DE-05379-01 Morphogenesis and maturation of craniofacial sutures (animals)
R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)
R13DE-05752-01 Conference on biology of mineralized connective tissues
** R23DE-05793-01 Degradation of collagen in inflammation (human gingiva)
R23DE-05956-01 The adhesive of Mytilus edulis
R23DE-05967-01 Role of prostaglandin E in periodontal disease activity

ALBUMINOIDS, COLLAGEN, PROCOLLAGEN

- ** P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)
P50DE-02623-14 0026 Center for oral health research - Collagen biosynthesis in the periodontium
R01DE-03318-10 The molecular nature of gingival and mucosal collagen (rat)
R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)
** R01DE-05690-01 Localization of the procollagens in dental tissues

ALBUMINOIDS, ELASTIN

- P50DE-02623-14 0026 Center for oral health research - Collagen biosynthesis in the periodontium
R01DE-03223-11 Kinetics of mineralization of teeth (human)

ALBUMINOIDS, KERATIN

- SEE ALSO ALBUMINOIDS, KERATOHYALIN
P50DE-02600-15 0032 Support for oral biology research center - Keratohyalin in keratinization of oral mucosa and skin (human, rats)
R01DE-05190-03 Factors determining variation in adult oral mucosa

ALBUMINOIDS, KERATOHYALIN

- ** P50DE-02600-15 0032 Support for oral biology research center - Keratohyalin in keratinization of oral mucosa and skin (human, rats)
** R01DE-04660-06 Keratohyalin in keratinization-Dral mucosa and skin (human)
R01DE-05999-01 The role of nutrition in oral health

ALBUMINS

- R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)
N01DE-12430-00 Investigation of anticaries vaccine in primates

ALBUMINS, CONALBUMIN

- R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

ALCOHOL CONSUMPTION

SEE ALCOHOLISM - DRINKING, ALCOHOL CONSUMPTION

ALCOHOLISM - DRINKING, ALCOHOL CONSUMPTION

- ** P50DE-02568-15 0212 Regional dental research center - Determination of risk related to alcohol consumption before pregnancy recognition

ALDEHYDES

- P50DE-02668-15 0125 Regional dental research center - Collagen crosslinks and the fate of extracellular matrix

ALDEHYDES, FORMALDEHYDE

- R23DE-05886-01 Organic oligomers for new hydrophobic dental cements

ALDOSTERONE STIMULATING FACTOR ANT PIT

SEE PITUITARY-DIENCEPHALON HORMONES, ACTH

ALEXIN

SEE IMMUNOLOGY, COMPLEMENT

ALIMENTARY TRACT

SEE GASTROINTESTINAL SYSTEM (GENERAL)

ALKALINE PHOSPHATASE

SEE PHOSPHOMONESTERASES, ALKALINE PHOSPHATASE

ALKALOIDS, COLCHICINE

- R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)

ALKALOIDS, MORPHINES

- R01DE-05369-03 Factors affecting dental postoperative pain

ALKALOIDS, MORPHINES, NALOXONE

- R01DE-04786-04 Dental and orofacial pain-Brain stem mechanisms (cats)
R01DE-05204-03 Operant neural control in trigeminal pain systems (rats)
R01DE-05369-03 Factors affecting dental postoperative pain

ALKALOIDS, OPIUM AND OPIATES

- SEE ALSO ALKALOIDS, MORPHINES
** R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)

ALKALOIDS, PILOCARPINE TYPE

- R01DE-05632-01 Development of salivary gland secretory function (rats)

N-ALKYLAMINO ACIDS

SEE AMINO ACIDS, N-ALKYLAMINO ACIDS

ALKYLATING AGENTS

- R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

ALKYL TRANSFER, TRANSMETHYLATION

- R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)

ALLELES

SEE GENETICS, GENES, ALLELES

ALLERGY

SEE HYPERSENSITIVITY (GENERAL)

ALLERGY AND IMMUNOLOGY STUDY SECTION

- ** R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)

ALLOANTIGENS

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

ALLOANTISERA

SEE IMMUNITY, IMMUNOSUPPRESSION, ALLOANTISERA

ALLOGENIC DISEASE

SEE TISSUE COMPATIBILITY-TRANSPLANT, GRAFT VERSUS HOST REACTIONS

ALLOGENIC TRANSPLANTATION

SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION HETEROLOGOUS
SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION HOMOLOGOUS

ALLOGENIC INHIBITION, ANTISERA

SEE IMMUNITY, IMMUNOSUPPRESSION, ALLOANTISERA

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

ALLOGRAFT
SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION
HOMOLOGOUS

ALLOIMMUNITY
SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOIMMUNITY

ALLOYS
SEE METALS, ALLOYS

ALPHAHERPESVIRINAE
SEE VIRUSES, HERPESVIRIDAE, ALPHAHERPESVIRINAE

ALPHA RECEPTORS
SEE NEUROTRANSMITTERS RECEPTORS, ADRENERGIC
RECEPTORS, ALPHA RECEPTORS

**ALPHA WAVE (BIOFEEDBACK)
CONDITIONING**
SEE PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL
CONTROL

ALTITUDE
SEE ENVIRONMENT, ALTITUDE

ALUMINA
SEE METALS, ALUMINUM (COMPOUNDS), ALUMINUM OXIDE

ALUMINUM
SEE METALS, ALUMINUM (COMPOUNDS)

ALUMINUM (COMPOUNDS)
SEE METALS, ALUMINUM (COMPOUNDS)

ALUMINUM OXIDE
SEE METALS, ALUMINUM (COMPOUNDS), ALUMINUM OXIDE

ALVEOLUS, DENTAL
SEE DENTAL STRUCTURE, DENTAL ALVEOLUS

ALVEOLUS, LUNG
SEE RESPIRATORY SYSTEM, LUNG ALVEOLUS

AMALGAM
SEE DENTAL MATERIALS, AMALGAM DENTAL

AMELOBLASTS
SEE DENTAL STRUCTURE, AMELOBLASTS

AMERICAN TYPE CULTURE COLLECTION
SEE TISSUE (CELL) CULTURE, CELL CULTURE COLLECTIONS
BANKS AND REGISTRIES

AMES MUTAGEN TEST
SEE GENETICS, MUTAGENS, MUTAGEN TESTS

AMIDES, UREA
R01DE-05505-02 Periodontitis and host defense in juvenile
diabetes (human)

AMIDINE-LYASES, ADENYLOSUCCINATE LYASE
R01DE-04657-05 Abnormal palatal development induced by
hadacidin (fungi)

AMIDOBENZENES
SEE PHENYLAMIDES

AMINE HORMONES
SEE CHOLINE, ACETYLCHOLINE
SEE PHENYLALKYLAMINES, CATECHOLAMINES, EPINEPHRINE
SEE PHENYLALKYLAMINES, CATECHOLAMINES,
NOREPINEPHRINE

AMINES, BIOGENIC, NEURAL
SEE NEUROTRANSMITTERS AND NEUROMODULATORS
(GENERAL)

AMINES, POLYAMINES
R01DE-03715-06 Cellular assembly--Its role in facial
morphogenesis (fungi)

AMINO ACIDS, N-ALKYLAMINO ACIDS
R01DE-01830-19 Quantitation of enamel demineralization
mechanisms

AMINO ACIDS, GAMMA-AMINOBUTYRIC ACID
R01DE-03459-10 Teratogens effects on cleft palate formation
(mice)
R01DE-05390-03 Opiate action on CNS terminals of tooth pulp
fibers (animals)

**AMINO ACIDS, ETHYLENEDIAMINO ACIDS,
EDTA**
R01DE-01830-19 Quantitation of enamel demineralization
mechanisms
R01DE-04926-04 Bacterial coaggregation mechanisms in
dental plaque

AMINO ACIDS SEQUENCE
SEE PROTEINS-PEPTIDES STRUCTURE, AMINO ACIDS SEQUENCE

GAMMA-AMINOBUTYRIC ACID
SEE AMINO ACIDS, GAMMA-AMINOBUTYRIC ACID

AMINOPOLYSACCHARIDES
SEE POLYSACCHARIDES, GLYCOSAMINOGLYCANS

AMINO SUGARS
SEE CARBOHYDRATES, AMINO SUGARS

AMINOSULFONIC ACIDS
SEE ALSO SULFONAMIDES
R01DE-05476-02 Novel peptide derived sweeteners

AMMONIUM QUATERNARY
R01DE-05327-03 Polymeric polyphosphonates on dental caries
and plaque (rats)

AMP CYCLIC
SEE PURINE NUCLEOTIDES, ADENINE NUCLEOTIDES, AMP
CYCLIC

AMYLASE
SEE CARBOHYDRASES, AMYLASE

ALPHA-AMYLASE
SEE CARBOHYDRASES, ALPHA-AMYLASE

AMYLO-ALPHA 1,4-GLYCOSIDASE
SEE CARBOHYDRASES, ALPHA 1,4-GLUCAN GLUCOHYDROLASE

ANABOLIC FACTORS
SEE GROWTH FACTORS (INCL. ANABOLICS)

ANAEROBES, BACTERIAL
SEE MICROORGANISMS, ANAEROBES

ANAEROBIC MICROORGANISMS
SEE MICROORGANISMS, ANAEROBES

ANALGESIA
SEE SENSORY DEPRESSION, ANALGESIA

ANALGESICS
SEE NEUROPHARMACOLOGICAL AGENTS, ANALGESICS

ANALOGS OF CARBOHYDRATES
SEE CARBOHYDRATES ANALOGS

ANALOGS OF ENZYME SUBSTRATES
SEE ENZYME SUBSTRATE ANALOGS

ANALOGS OF METHOTREXATE
SEE FOLIC ACID ANTAGONISTS, METHOTREXATE

ANALOGS OF NUCLEOSIDES
SEE NUCLEOSIDES ANALOGS

ANALOGS OF PHENYLALANINE
SEE CYCLIC AMINO ACIDS, PHENYLALANINE ANALOGS

ANALOGS OF PROSTAGLANDINS
SEE FATTY ACIDS, UNSATURATED, PROSTAGLANDINS ANALOGS

ANALOGS OF PYRIDOXAL
SEE VITAMIN B6, PYRIDOXAL ANALOGS

ANALOGS OF VITAMIN A
SEE VITAMIN A ANALOGS

ANALYSIS AND/OR EVALUATION
SEE HEALTH CARE (SERVICES) (RESOURCES) ANALYSIS AND
EVALUATION

ANALYTICAL CHEMISTRY
SEE CHEMISTRY, ANALYTICAL

ANATOMY (GENERAL)*
SEE ALSO BODY PHYSICAL CHARACTERISTICS (GENERAL)
** P01DE-01697-19 0038 A research program in craniofacial
problems - Anatomy of the posterior pharyngeal wall
** P01DE-02872-12 0061 Craniofacial dysmorphology -
Craniofacial dysmorphology
** R01DE-05078-05 Craniofacial growth and remodeling
(human)
** P01DE-05837-01 0003 Growth, surgical, and speech aspects
of cleft palate - Speech physiology and anatomy (children,
adults)

ANATOMY MICROSCOPIC (HISTOLOGY)
SEE HISTOLOGY (GENERAL)*

ANDROGENS
SEE ANDROSTANE SERIES, ANDROGENS

ANDROSTANE SERIES, ANDROGENS
** P50DE-02668-15 0213 Regional dental research center -
Hormone action is the salivary glands of inbred mice
R01DE-04039-04 Sex steroid metabolism in oral tissues

ANDROSTANE SERIES, TESTOSTERONE
R23DE-05072-03 Stimulation of regenerating rat
submandibular glands

ANENCEPHALUS
SEE CONGENITAL ABNORMALITIES, BRAIN, ANENCEPHALUS

ANESTHESIA, DENTAL
SEE SENSORY DEPRESSION, ANESTHESIA DENTAL

ANESTHESIA, ELECTROANESTHESIA
SEE SENSORY DEPRESSION, ANALGESIA BY MASKING,
ELECTROANALGESIA

ANESTHESIA, INHALATION
SEE SENSORY DEPRESSION, ANESTHESIA (GENERAL),
INHALATION

ANESTHESIA COMPLICATIONS
SEE DISEASES, COMPLICATIONS, ANESTHESIA RELATED

ANESTHESIOLOGY
SEE HEALTH SCIENCES PROFESSIONS, ANESTHESIOLOGY

ANGIOGENESIS
SEE CARDIOVASCULAR SYSTEM, ANGIOGENESIS

ANGIOTENSIN II
SEE PEPTIDES, VASOACTIVE PEPTIDES, ANGIOTENSIN II

ANILIDES
SEE PHENYLAMIDES

ANIMAL AGE AND LIFE STAGES
SEE AGE (ANIMAL)

ANIMAL BEHAVIOR
SEE PSYCHOLOGY, BEHAVIOR ANIMAL

ANIMAL FEEDS
SEE FOOD, ANIMAL FEEDS

ANIMAL HUSBANDRY
SEE ANIMALS, VETERINARY SCIENCE

ANIMALS (SEE SPECIFIC ANIMALS)
SEE AGE (ANIMAL)
SEE PSYCHOLOGY, BEHAVIOR ANIMAL

ANIMALS, VETERINARY MEDICINE
N01DE-52452-12 Oral facial malformations in the rhesus
monkey

ANIMALS, VETERINARY SCIENCE
SEE ALSO FOOD, DAIRY PRODUCTS
N01DE-52452-12 Oral facial malformations in the rhesus
monkey

ANION
SEE IONS, ANION

ANKYLOSIS
SEE SKELETAL DISORDERS, ANKYLOSIS

ANTAGONISM
SEE DRUGS AND PHYSICAL AND/OR CHEMICAL AGENTS
INTERACTION
SEE DRUGS INTERACTION
SEE PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION
(BIOLOGICAL AND ECOLOGICAL)

ANTHROPOLOGY, PHYSICAL
SEE BODY PHYSICAL CHARACTERISTICS (GENERAL)

ANTHROPOMETRY
SEE BODY PHYSICAL CHARACTERISTICS (GENERAL)

ANTIADRENERGICS
SEE NEUROPHARMACOLOGICAL AGENTS, SYMPATHOLYTIC

ANTIBACTERIAL AGENTS
SEE COMMUNICABLE DISEASE CONTROL AGENTS,
ANTIBACTERIAL

ANTIBIOTICS
SEE ALSO COMMUNICABLE DISEASE CONTROL AGENTS
P01DE-02847-13 0021 Microbial ecology and its relation to
dental disease - Acquisition, transmission and localization of
human oral bacteria (rodents)
P50DE-04898-05 0003 Periodontal disease research center -
Therapy and prevention of periodontal diseases (human)
** R01DE-05622-01 Rx for dental patients at risk for
endocarditis (dentists)
** R01DE-05634-01 Antibiotic resistance transfer in oral
streptococci (human)
N01DE-92422-04 Dental plaque and saliva from gastric
intubated patients

ANTIBIOTICS, ACTINOMYCIN D
R01DE-05678-02 Salivary changes after cancer
chemotherapeutic drugs

**ANTIBIOTICS, AMINOGLYCOSIDE ANTIBIOTICS,
KANAMYCIN**
R01DE-05334-02 Periodontal therapy by controlled local drug
delivery (human)

**ANTIBIOTICS, ANTHRACYCLINES,
ADRIAMYCIN**
R01DE-05678-02 Salivary changes after cancer
chemotherapeutic drugs

ANTIBIOTICS, BACTERIOCINS
SEE ALSO IMMUNOLOGY, ANTIGENS BACTERIAL
P01DE-02847-13 0022 Microbial ecology and its relation to
dental disease - Cemental caries as a dental problem (human,
rats, primates)
R01DE-04224-07 Genetics of oral microflora

ANTIBIOTICS, LINCOMYCIN, CLINDAMYCIN
R01DE-06070-01 Antibiotic susceptibilities of periodontal
bacteria

**ANTIBIOTICS, MACROLIDE ANTIBIOTICS,
ERYTHROMYCIN**
R01DE-06070-01 Antibiotic susceptibilities of periodontal
bacteria

ANTIBIOTICS, NYSTATIN
R01DE-05334-02 Periodontal therapy by controlled local drug
delivery (human)

ANTIBIOTICS, PENICILLIN
R01DE-06070-01 Antibiotic susceptibilities of periodontal
bacteria

ANTIBIOTICS, TETRACYCLINE
P50DE-04898-05 0003 Periodontal disease research center -
Therapy and prevention of periodontal diseases (human)
R01DE-05334-02 Periodontal therapy by controlled local drug
delivery (human)

(cont'd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M. Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number

- APTHOUS STOMATITIS**
SEE ORAL-PHARYNGEAL DISORDERS, STOMATITIS, APHTHOUS
- APLASIA (BRAIN)**
SEE CONGENITAL ABNORMALITIES, BRAIN, ANENCEPHALUS
- APPOINTMENTS AND VISITS (PATIENTS)**
SEE HEALTH CARE (SERVICES) (RESOURCES) UTILIZATION, APPOINTMENTS-VISITS
- AQUATIC ORGANISMS, MARINE**
SEE WATER ENVIRONMENT, AQUATIC ORGANISMS, MARINE*
- AQUEORIN**
SEE PROTEINS, CALCIUM BINDING PROTEINS
- ARABINONUCLEOSIDES**
SEE NUCLEOSIDES, ARABINONUCLEOSIDES
- ARABINOSYLADEININE**
SEE PURINE NUCLEOSIDES, ADENINE NUCLEOSIDES, ADENINE ARABINOSIDE
- ARACHIDONIC ACID**
SEE FATTY ACIDS, ARACHIDONIC ACID
- ARACHNODACTYL**
SEE METABOLIC DISORDERS INBORN, MARFAN SYNDROME
- ARGININE**
SEE DIAMINO ACIDS, ARGININE
- ARNOLD-CHIARI DEFORMITY**
SEE CONGENITAL ABNORMALITIES, BRAIN, CEREBELLOMEDULLARY DYSPLASIA
- AROUSAL**
SEE PSYCHIC ACTIVITY LEVEL, AROUSAL
- ARTERENOL**
SEE PHENYLALKYLAMINES, CATECHOLAMINES, NOREPINEPHRINE
- ARTERIAL BLOOD PRESSURE**
SEE CARDIOVASCULAR FUNCTION, BLOOD PRESSURE
- ARTHRITIS**
SEE SKELETAL DISORDERS, ARTHRITIS
- ARTHRITIS, RHEUMATOID**
SEE SKELETAL DISORDERS, ARTHRITIS, RHEUMATOID
- ARTHROPLASTY**
SEE SKELETAL DISORDERS, ORTHOPEDICS, ARTHROPLASTY
- ARTHUS PHENOMENON**
SEE HYPERSENSITIVITY, ANAPHYLAXIS, ARTHUS PHENOMENON
- ARTIFICIAL FOODS**
SEE FOOD SCIENCES AND TECHNOLOGY, SYNTHETIC FOODS
- ARTIFICIAL INTELLIGENCE**
SEE COMPUTER, ARTIFICIAL INTELLIGENCE, PATTERN RECOGNITION AND CONTROL SYSTEMS
- ARTIFICIAL TOOTH SOCKET IMPLANT**
SEE DENTAL PROSTHESIS, DENTAL IMPLANT ENDOSSEOUS
- ARYLSULFATASES**
SEE SULFATASES, ARYLSULFATASES
- ASCORBIC ACID, ASCORBATE**
SEE VITAMIN C
- ASPARTIC ACID**
SEE DICARBOXYLIC AMINO ACIDS, ASPARTIC ACID
- ASPIRIN**
SEE PHENYL CARBOXYLATES, SALICYLATES, ACETYL-
- ASSAY**
SEE BIOASSAY*
SEE RADIOASSAY (RADIOMETRY)
- ASTHMA**
SEE HYPERSENSITIVITY, RESPIRATORY HYPERSENSITIVITY, ASTHMA
- ASTIGMATISM**
SEE EYE REFRACTIVE DISORDERS, ASTIGMATISM
- ATAXIA AND DYSKINESIA (CEREBELLAR)**
SEE CONGENITAL ABNORMALITIES, BRAIN, CEREBELLOMEDULLARY DYSPLASIA
- ATP**
SEE PURINE NUCLEOTIDES, ADENINE NUCLEOTIDES, ATP
- ATP:ADENOSINE-5-PHOSPHOTRANSFERASE**
SEE PHOSPHOTRANSFERASES, ADENOSINE KINASE
- ATPASE**
SEE PHOSPHATASES, ADENOSINE TRIPHOSPHATASE
- ATP PHOSPHOHYDROLASE**
SEE PHOSPHATASES, ADENOSINE TRIPHOSPHATASE
- ATP:PYRUVATE PHOSPHOTRANSFERASE**
SEE PHOSPHOTRANSFERASES, ATP:PYRUVATE PHOSPHOTRANSFERASE
- ATTITUDE TO HEALTH AND HEALTH PROBLEMS**
SEE PSYCHOLOGY, ATTITUDE TO HEALTH AND HEALTH PROBLEMS
- ATTITUDES**
SEE PSYCHOLOGY, ATTITUDES (AND RELATED)
- ANT**
R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
** R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)
- ANTIBIOTICS, VALINOMYCIN**
R01DE-02110-17 Salivary gland structure and function (rats)
- ANTIBODIES**
SEE IMMUNOLOGY, ANTIBODIES
- ANTIBODIES, BACTERIAL**
SEE IMMUNOLOGY, ANTIBODIES BACTERIAL
- ANTIBODIES, VIRAL**
SEE IMMUNOLOGY, ANTIBODIES VIRAL
- ANTIBODY-ANTIGEN REACTIONS**
SEE IMMUNOLOGY, ANTIGEN-ANTIBODY REACTIONS
- ANTIBODY-ANTIGEN REACTIONS IN VITRO**
SEE IMMUNOLOGY, SEROLOGY*
- ANTIBODY BIOSYNTHESIS**
SEE IMMUNOLOGY, ANTIBODY FORMATION
- ANTIBODY FORMATION**
SEE IMMUNOLOGY, ANTIBODY FORMATION
- ANTIBODY RECEPTORS**
SEE IMMUNOLOGY, ANTIBODIES, ANTIBODY RECEPTORS
- ANTI-CARIES VACCINE**
SEE VACCINES, BACTERIAL, ANTI-CARIES VACCINE
- ANTICHOLINERGIC AGENTS**
SEE NEUROPHARMACOLOGICAL AGENTS, PARASYMPATHOLYTIC
- ANTICONSULSANTS**
SEE NEUROPHARMACOLOGICAL AGENTS, ANTICONSULSANTS
- ANTIDROMIC IMPULSES**
SEE NEUROPHYSIOLOGY, NEURAL TRANSMISSION, ANTIDROMIC IMPULSES
- ANTIGEN-ANTIBODY REACTIONS**
SEE IMMUNOLOGY, ANTIGEN-ANTIBODY REACTIONS
- ANTIGEN-ANTIBODY REACTIONS IN VITRO**
SEE IMMUNOLOGY, SEROLOGY*
- ANTIGENIC DETERMINANTS**
SEE IMMUNOLOGY, ANTIGENS
- ANTIGENIC DETERMINANTS OF V REGION**
SEE IMMUNOGNETICS, IMMUNOGLOBULIN GENES AND CONTROL
- ANTIGENS**
SEE IMMUNOLOGY, ANTIGENS
- ANTIGENS BACTERIAL**
SEE IMMUNOLOGY, ANTIGENS BACTERIAL
- ANTIGENS MICROBIAL**
SEE IMMUNOLOGY, ANTIGENS MICROBIAL
- ANTIGENS VIRAL**
SEE IMMUNOLOGY, ANTIGENS VIRAL
- ANTIINFECTIVE AGENTS**
SEE COMMUNICABLE DISEASE CONTROL AGENTS
- ANTIINFECTIVE AGENTS, ANTIBACTERIAL**
SEE COMMUNICABLE DISEASE CONTROL AGENTS, ANTIBACTERIAL
- ANTIINFLAMMATORY AGENTS**
SEE DISEASES, PATHOLOGIC PROCESSES, INFLAMMATION, ANTIINFLAMMATORY AGENTS
- ANTIMICROBIAL AGENTS**
SEE COMMUNICABLE DISEASE CONTROL AGENTS
- ANTIMUSCARINIC AGENTS**
SEE NEUROPHARMACOLOGICAL AGENTS, PARASYMPATHOLYTIC
- ANTINEOPLASTIC AGENTS COMBINATION**
SEE NEOPlastic THERAPY, COMBINATION ANTINEOPLASTIC THERAPY
- ANTIOXIDANTS**
SEE OXIDANTS, ANTIOXIDANTS
- ANTITHROMBIN**
SEE BLOOD COAGULATION, ANTITHROMBINS
- ANTITHROMBINS**
SEE BLOOD COAGULATION, ANTITHROMBINS
- ANTIVIRAL AGENTS**
SEE COMMUNICABLE DISEASE CONTROL AGENTS, ANTIVIRAL
- ANTIVIRAL ANTIBODIES**
SEE IMMUNOLOGY, ANTIBODIES VIRAL
- ANXIETY**
SEE PSYCHOLOGY, EMOTIONS, ANXIETY
- ANXIETY, DENTAL**
SEE DENTAL FEAR AND ANXIETY
- APATITES**
SEE CALCIUM PHOSPHATES, APATITES
- APERT'S SYNDROME**
SEE CONGENITAL ABNORMALITIES, SKELETAL, ACROCEPHALOSYNDACTYLIA

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
**Oriented significantly to above subject.

AU

SEE METALS, HEAVY METALS, GOLD (COMPOUNDS)

AUDIOTAPES

SEE INFORMATION AND COMMUNICATION, AUDIOTAPES

AUDITORY NERVE

SEE NERVOUS SYSTEM, CRANIAL NERVES, ACOUSTIC NERVE

AUDITORY PATHWAYS

SEE BRAIN, AUDITORY PATHWAYS

AUTOGENEIC TRANSPLANTATION

SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION AUTOLOGOUS

AUTOGENIC CONDITIONING (TRAINING)

SEE PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL CONTROL

AUTOGRAFT

SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION AUTOLOGOUS

AUTOIMMUNE FOREIGN TRANSPLANT DISEASE

SEE TISSUE COMPATIBILITY-TRANSPLANT, GRAFT VERSUS HOST REACTIONS

AUTOLOGOUS TRANSPLANTATION

SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION AUTOLOGOUS

AUTOLYSIS

SEE DISEASES, PATHOLOGIC PROCESSES, AUTOLYSIS

AUTOMATED ANALYTICAL PROCESSING AND CONTROL SYSTEMS

SEE BIOMEDICAL SYSTEMS AUTOMATED

AUTOMATED BIOMEDICAL FACILITIES

SEE BIOMEDICAL SYSTEMS AUTOMATED

AUTOMATED HEALTH RECORDS (SYSTEMS)

SEE HEALTH RECORDS (SYSTEMS) AUTOMATED

AUTONOMIC CONDITIONING

SEE PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL CONTROL

AUTONOMIC NERVOUS SYSTEM

SEE NERVOUS SYSTEM AUTONOMIC

AUTOPROTHROMBIN III

SEE BLOOD COAGULATION, FACTOR X

AUTORADIOGRAPHY

SEE RADIOAUTOGRAPHY*

AUTOTRANSPLANTATION

SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION AUTOLOGOUS

AXONS

SEE NERVOUS SYSTEM, NEURONS, AXONS

AZEPINES, DIAZEPINES, DIAZEPAM

R01DE-03469-10 Teratogens effects on cleft palate formation (mice)
R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)

B LOCUS (CHICKEN)

SEE IMMUNOGNETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)

B-TYPE VIRUSES

SEE VIRUSES, RETROVIRIDAE

BA

SEE METALS, ALKALINE EARTH METALS, BARIUM (COMPOUNDS)

BABY FOODS

SEE FOOD, INFANT FOODS

BACILLUS PILIFORMIS

SEE BACTERIA, GRAM-NEGATIVE*

BACTERIA (GENERAL)*

SEE ALSO MICROBIAL ORAL FLORA

- ** P50DE-02623-14 0023 Center for oral health research - Interactions of oral bacteria and polymorphonuclear leukocytes
** P50DE-02731-15 0021 Development support for dental research institute - Bacterial specificity in periodontal disease
** R01DE-04504-03 Plaque bacteria as predictors of human dental caries
R23DE-05331-01 Local host mechanism in periodontal disease (human, monkeys)
** R01DE-05427-01 Adherence mechanisms of oral microbes
** R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence
** R01DE-05462-01 Saliva mediated aggregation of oral bacteria (human)
** R01DE-05560-01 Rapid identification of oral bacteria
R01DE-05640-01 Cytotoxicity of periodontopathic bacteria
** R01DE-05652-01 Biological role of lysozyme in human saliva
** R01DE-05773-01 Ligand receptor interactions of cariogenic bacteria
** R23DE-05887-01 Effects of oral bacteria on epithelium in vitro

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

(contd).

- ** R01DE-06070-01** Antibiotic susceptibilities of periodontal bacteria
- ** N01DE-92418-05** Characterize and identify pleomorphic oral bacteria
- BACTERIA, ACTINOMYCETALES***
- ** R01DE-05706-01** Role of microbial collagenases in periodontal disease
- BACTERIA, ACTINOMYCETALES, ACTINOMYCES***
- ** P50DE-02600-15 0040** Support for oral biology research center - Fate of actinomyces viscosus components within phagocytic cells
- P50DE-02623-14 0005** Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- P50DE-02731-15 0035** Development support for dental research institute - Immune regulation in periodontal disease
- P01DE-02847-13 0021** Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)
- ** R01DE-04174-07** Variations in the surface structures of oral bacteria
- ** R01DE-04175-07** Variations in the surface structures of oral bacteria
- R01DE-04614-05** Adherence of oral streptococci to hydroxyapatite
- R01DE-04721-04** Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- R01DE-04744-04** New antimicrobial agents for preventing oral diseases
- P50DE-04898-05 0001** Periodontal disease research center - Microbiology (human)
- P50DE-04898-05 0002** Periodontal disease research center - Host response in periodontal disease (human)
- R01DE-04926-04** Bacterial coaggregation mechanisms in dental plaque
- P50DE-05139-04 0001** Clinical research center for periodontal disease - Microbiology
- P50DE-05139-04 0002** Clinical research center for periodontal disease - Immunological investigations
- R01DE-05652-01** Biological role of lysozyme in human saliva
- ** R01DE-05729-01** Etiological mechanisms in periodontal disease
- R23DE-05809-01** Effects of fluoride on physiology of oral bacteria
- ** R01DE-05991-01** Mechanisms of virulence of oral periodontopathogens
- N01DE-12430-00** Investigation of anticaries vaccine in primates
- N01DE-72408-06** Cross-reacting antigens/oral flora acidogenic bacteria
- N01DE-92418-05** Characterize and identify pleomorphic oral bacteria
- BACTERIA, ACTINOMYCETALES, BACTERIONEMA***
- R01DE-04439-04** Dental calculus formation using calcifiable lipoprotein analogues
- N01DE-92418-05** Characterize and identify pleomorphic oral bacteria
- BACTERIA, ACTINOMYCETALES, LEPTOTRICHIA***
- P50DE-04898-05 0001** Periodontal disease research center - Microbiology (human)
- P50DE-04898-05 0002** Periodontal disease research center - Host response in periodontal disease (human)
- P50DE-05139-04 0002** Clinical research center for periodontal disease - Immunological investigations
- N01DE-92418-05** Characterize and identify pleomorphic oral bacteria
- BACTERIA, ACTINOMYCETALES, ROTHIA DENTOCARIOSA**
- N01DE-92418-05** Characterize and identify pleomorphic oral bacteria
- BACTERIA, BACTEROIDACEAE, BACTEROIDES***
- R01DE-03488-10** Microbial composition of developing dental plaque
- R01DE-04721-04** Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- P50DE-04898-05 0001** Periodontal disease research center - Microbiology (human)
- R01DE-05123-04** Periodontopathic bacteria:chemical-biologic nature (mammals)
- P50DE-05139-04 0002** Clinical research center for periodontal disease - Immunological investigations
- R01DE-05706-01** Role of microbial collagenases in periodontal disease
- R23DE-05887-01** Effects of oral bacteria on epithelium in vitro
- N01DE-92418-05** Characterize and identify pleomorphic oral bacteria
- BACTERIA, BACTEROIDACEAE, BACTEROIDES MELANINOGENICUS***
- P50DE-02623-14 0005** Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- P50DE-02731-15 0035** Development support for dental research institute - Immune regulation in periodontal disease
- P01DE-02847-13 0020** Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
- P50DE-04898-05 0002** Periodontal disease research center - Microbiology (human)
- P50DE-05139-04 0002** Clinical research center for periodontal disease - Immunological investigations
- N01DE-92418-05** Characterize and identify pleomorphic oral bacteria
- BACTERIA, BRUCELLACEAE***
- P50DE-02623-14 0005** Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- BACTERIA, CORYNEFORM GROUP, CORYNEBACTERIUM***
- N01DE-92418-05** Characterize and identify pleomorphic oral bacteria
- BACTERIA, ENTEROBACTERIACEAE, ESCHERICHIA COLI***
- P50DE-05139-04 0002** Clinical research center for periodontal disease - Immunological investigations
- BACTERIA, GRAM-NEGATIVE***
- SEE ALSO BACTERIA, BRUCELLACEAE***
- P50DE-02600-15 0039** Support for oral biology research center - Saliva in abnormal bacterial adherence and colonization (human)
- P50DE-02600-15 0041** Support for oral biology research center - Perio treatment (human)
- R01DE-03488-10** Microbial composition of developing dental plaque
- R01DE-04721-04** Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- ** R01DE-04808-02** Virulence factors of gram negative corroding bacteria
- ** R01DE-05123-04** Periodontopathic bacteria:chemical-biologic nature (mammals)
- P50DE-05139-04 0002** Clinical research center for periodontal disease - Immunological investigations
- R01DE-05252-01** Bidirectional effects of subgingival dental plaque
- R01DE-05640-01** Cytotoxicity of periodontopathic bacteria
- BACTERIA, GRAM-POSITIVE***
- SEE ALSO BACTERIA, ACTINOMYCETALES, ACTINOMYCES***
- SEE ALSO BACTERIA, ACTINOMYCETALES, BACTERIONEMA***
- SEE ALSO BACTERIA, STREPTOCOCCACEAE***
- P50DE-05139-04 0002** Clinical research center for periodontal disease - Immunological investigations
- R01DE-05252-01** Bidirectional effects of subgingival dental plaque
- BACTERIA, LACTOBACILLACEAE, LACTOBACILLUS***
- ** R01DE-04174-07** Variations in the surface structures of oral bacteria
- ** R01DE-04175-07** Variations in the surface structures of oral bacteria
- P50DE-04898-05 0001** Periodontal disease research center - Microbiology (human)
- N01DE-12430-00** Investigation of anticaries vaccine in primates
- N01DE-72408-06** Cross-reacting antigens/oral flora acidogenic bacteria
- BACTERIA, NEISSERIAACEAE, NEISSERIA***
- R23DE-05887-01** Effects of oral bacteria on epithelium in vitro
- BACTERIA, NEISSERIAACEAE, VEILLONELLA***
- P50DE-04898-05 0001** Periodontal disease research center - Microbiology (human)
- P50DE-05139-04 0002** Clinical research center for periodontal disease - Immunological investigations
- BACTERIA, PROPIONIBACTERIACEAE, PROPIONIBACTERIUM***
- P50DE-04898-05 0001** Periodontal disease research center - Microbiology (human)
- BACTERIA, PSEUDOMONADALES, SPIRILLACEAE***
- SEE ALSO BACTERIA, PSEUDOMONADALES, VIBRIO***
- P01DE-02847-13 0020** Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
- P50DE-04898-05 0001** Periodontal disease research center - Microbiology (human)
- BACTERIA, PSEUDOMONADALES, VIBRIO***
- P01DE-02847-13 0020** Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
- P50DE-05139-04 0001** Clinical research center for periodontal disease - Microbiology
- BACTERIA, SPIROCHETES***
- P50DE-02600-15 0041** Support for oral biology research center - Perio treatment (human)
- R01DE-03488-10** Microbial composition of developing dental plaque
- ** R01DE-04645-04** A genetic-biochemical analysis of spirochete motility
- P50DE-05139-04 0001** Clinical research center for periodontal disease - Microbiology
- ** R01DE-05144-03** Periodontal disease--Role of spirochetes (rabbits, human)
- ** R01DE-05723-01** Spirochete influence on immunity in oral disease
- BACTERIA, SPIROCHETES, LEPTOSPIRA***
- R01DE-04645-04** A genetic-biochemical analysis of spirochete motility
- BACTERIA, SPIROCHETES, TREPONEMA***
- R01DE-04645-04** A genetic-biochemical analysis of spirochete motility
- R01DE-04721-04** Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- P50DE-05139-04 0001** Clinical research center for periodontal disease - Microbiology
- BACTERIA, SPIROCHETES, TREPONEMA PALLIDUM***
- R01DE-05723-01** Spirochete influence on immunity in oral disease
- BACTERIA, STREPTOCOCCACEAE***
- ** R01DE-04614-05** Adherence of oral streptococci to hydroxyapatite
- BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS***
- ** P50DE-02731-15 0019** Development support for dental research institute - Structure and maintenance of extrachromosomal DNA in streptococci
- ** R01DE-03180-11** Microbiologic studies of the human oral streptococci
- ** R01DE-04174-07** Variations in the surface structures of oral bacteria
- ** R01DE-04175-07** Variations in the surface structures of oral bacteria
- P50DE-04898-05 0001** Periodontal disease research center - Microbiology (human)
- R01DE-05634-01** Antibiotic resistance transfer in oral streptococci (human)
- R01DE-05652-01** Biological role of lysozyme in human saliva
- N01DE-72408-06** Cross-reacting antigens/oral flora acidogenic bacteria
- BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS, VIRIDANS GROUP***
- SEE ALSO BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS MITIS***
- SEE ALSO BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS SALIVARIUS***
- P50DE-02623-14 0014** Center for oral health research - Surface receptors on plaque forming organisms
- R01DE-03180-11** Microbiologic studies of the human oral streptococci
- BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS GROUP A***
- R01DE-02901-13** Cell wall antigens of cariogenic streptococci (human, rabbits)
- BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS MITIS***
- R01DE-03180-11** Microbiologic studies of the human oral streptococci
- R23DE-05887-01** Effects of oral bacteria on epithelium in vitro
- BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS MUTANS***
- ** P50DE-02670-15 0025** Institute of Dental Research - Biochemical basis for the cariogenic property of Streptococcus mutans (rat)
- ** P50DE-02670-15 0033** Institute of Dental Research - Genetic and biochemical basis for S mutans virulence (rats)
- P01DE-02847-13 0021** Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)
- ** R01DE-02901-13** Cell wall antigens of cariogenic streptococci (human, rabbits)
- ** R01DE-03118-11** Inhibition of saccharide metabolism by oral flora
- R01DE-03180-11** Microbiologic studies of the human oral streptococci
- ** R01DE-03258-10** Streptococcus mutans--Dental caries mechanism (human)
- ** R01DE-03487-10** Inhibition of human cariogenic streptococci
- R01DE-03578-10** Biosynthetic study of dental plaque polysaccharides
- R01DE-03654-09** Molecular basis of dental caries (human)
- ** R01DE-03758-07** Virulence characterization and immunization against S mutans (rats, rabbits)
- R01DE-04061-07** Salivary antibodies to S mutans--Induction and effects (monkeys)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects. See Appendix for investigator's name and Grant Number.

- ** R01DE-04217-07 Effective immunity to dental caries--Cellular basis
- R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)
- ** R01DE-04278-06 Human saliva-streptococcal metabolic interactions
- ** R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
- R01DE-04744-04 New antimicrobial agents for preventing oral diseases
- ** R01DE-04903-03 Trace metal uptake in cariogenic streptococcus mutants
- ** R01DE-05017-03 Characterization of surface antigens of S mutants
- ** R01DE-05180-03 Composition of S mutants in different growth environments
- ** R01DE-05359-01 Regulation of secretory immunity to S mutants (mice)
- ** R01DE-05696-01 Streptococcus mutants interaction with animal tissue (also human)
- ** R01DE-05747-01 Monoclonal antibody analysis of s. mutants antigens
- R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
- N01DE-12430-00 Investigation of anticaries vaccine in primates
- ** N01DE-62491-12 Use of mutants of cariogenic streptococci to prevent dental caries (rats)

BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS SALIVARIUS*

- R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)

BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS SANGUIS*

- P50DE-02623-14 0032 Center for oral health research - Interactions of salivary agglutinins and oral bacteria
- R01DE-03180-11 Microbiologic studies of the human oral streptococci
- R01DE-03731-06 Dextran sucrose of Streptococcus sanguis
- ** R01DE-04224-07 Genetics of oral microflora
- ** R01DE-04278-06 Human saliva-streptococcal metabolic interactions
- R01DE-04614-05 Adherence of oral streptococci to hydroxyapatite
- R01DE-04744-04 New antimicrobial agents for preventing oral diseases
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations
- ** R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)
- ** R01DE-05606-02 Pili of S sanguis and their role in adhesion (human, rabbits)
- R23DE-05809-01 Effects of fluoride on physiology of oral bacteria

BACTERIA, SPIRAL AND CURVED

SEE BACTERIA, PSEUDOMONADALES, SPIRILLACEAE*

BACTERIAL ANTIBODIES

SEE IMMUNOLOGY, ANTIBODIES BACTERIAL

BACTERIAL ANTIGENS

SEE IMMUNOLOGY, ANTIGENS BACTERIAL

BACTERIAL CAPSULE

- R01DE-04808-02 Virulence factors of gram negative corroding bacteria
- R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)

BACTERIAL DISEASES

SEE ALSO COMMUNICABLE DISEASE CONTROL AGENTS, ANTIBACTERIAL

SEE ALSO IMMUNOLOGY, ANTIBODIES BACTERIAL

SEE ALSO IMMUNOLOGY, ANTIGENS BACTERIAL

SEE ALSO TOXICOLOGY, BACTERIAL

- ** P50DE-02623-14 0005 Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- R01DE-05352-03 Immunochemical studies in periodontal disease
- R13DE-05753-01 Symposium on host-bacteria in periodontal diseases
- R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens

BACTERIAL DISEASES, ACTINOMYCETALES INFECTIONS

- ** R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)
- R01DE-05706-01 Role of microbial collagenases in periodontal disease

BACTERIAL DISEASES, ENTEROBACTERACEAE, SALMONELLA INFECTIONS

- R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)

BACTERIAL DNA

SEE NUCLEIC ACIDS, DNA BACTERIAL

BACTERIAL ENDOCARDITIS

SEE HEART DISORDERS, ENDOCARDITIS BACTERIAL

BACTERIAL POLYSACCHARIDES

SEE POLYSACCHARIDES, BACTERIAL (GENERAL)

BACTERIAL TOXICOLOGY

SEE TOXICOLOGY, BACTERIAL

BACTERIAL TOXINS

SEE IMMUNOLOGY, ANTIGENS BACTERIAL, BACTERIAL TOXINS (GENERAL)

BACTERIAL VACCINES

SEE VACCINES, BACTERIAL (GENERAL)

BACTERIAL VIRUSES

SEE VIRUSES, BACTERIOPHAGE*

BACTERICIDAL DEFENSES OF BODY (GENERAL)

SEE IMMUNITY, BACTERICIDAL DEFENSES (GENERAL)

BACTERICIDES

SEE COMMUNICABLE DISEASE CONTROL AGENTS, ANTIBACTERIAL

BACTERIOCINS

SEE ANTIBIOTICS, BACTERIOCINS

BACTERIOLOGY AND MYCOLOGY STUDY SECTION

- ** R01DE-03180-11 Microbiologic studies of the human oral streptococci
 - ** R01DE-03487-10 Inhibition of human cariogenic streptococci
 - ** R01DE-04808-02 Virulence factors of gram negative corroding bacteria
 - ** R01DE-05144-03 Periodontal disease--Role of spirochetes (rabbits, human)
 - ** R01DE-05218-03 DNA homologies among bacteria of periodontal diseases
 - ** R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)
 - ** R01DE-05606-02 Pili of S sanguis and their role in adhesion (human, rabbits)
- BACTERIOLYSIS**
SEE ALSO ANTIBIOTICS
SEE ALSO COMMUNICABLE DISEASE CONTROL AGENTS, ANTIBACTERIAL
P50DE-02623-14 0014 Center for oral health research - Surface receptors on plaque forming organisms

BACTERIONEMA

SEE BACTERIA, ACTINOMYCETALES, BACTERIONEMA*

BACTERIOPHAGE

SEE VIRUSES, BACTERIOPHAGE*

BACTERIOTROPINS

SEE IMMUNOLOGY, ANTIBODIES, OPSONINS

BACTEROIDES

SEE BACTERIA, BACTEROIDACEAE, BACTEROIDES*

BACTEROIDES MELANINOGENICUS

SEE BACTERIA, BACTEROIDACEAE, BACTEROIDES MELANINOGENICUS*

BARIUM (COMPOUNDS)

SEE METALS, ALKALINE EARTH METALS, BARIUM (COMPOUNDS)

BASEMENT MEMBRANE

SEE MEMBRANE, BASEMENT MEMBRANE

BASOLATERAL MEMBRANE

SEE CELL COMPONENTS, CELL MEMBRANE

BEHAVIOR

SEE PSYCHOLOGY, BEHAVIOR

BEHAVIOR, ANIMAL

SEE PSYCHOLOGY, BEHAVIOR ANIMAL

BEHAVIOR MODIFICATION (PSYCHOTHERAPY)

SEE PSYCHOTHERAPY, BEHAVIOR MODIFICATION

BEHAVIOR THERAPY

SEE PSYCHOTHERAPY, BEHAVIOR MODIFICATION

BEHAVIORAL MEDICINE

SEE ALSO HEALTH CARE SERVICES, PATIENT-PROFESSIONAL RELATIONS

SEE ALSO PSYCHOBIOLOGY, PSYCHOPHYSIOLOGY

SEE ALSO PSYCHOLOGY, ATTITUDE TO HEALTH AND HEALTH PROBLEMS

SEE ALSO PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL CONTROL

SEE ALSO PSYCHOPHYSIOLOGIC DISORDERS

SEE ALSO PSYCHOTHERAPY, BEHAVIOR MODIFICATION

SEE ALSO THERAPY COMPLIANCE

R01DE-04358-06 Treatment of temporomandibular joint pain

R01DE-04494-05 Control of stress during dental procedures (human)

** R01DE-04779-04 Behavioral stages for cleft palate patients

** R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)

** R23DE-05527-02 Behavioral treatments for nocturnal bruxism (human)

** R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)

** R23DE-05799-01 Behavioral methods for pedodontic management (human)

** R23DE-05858-01 Dentists' behavior and treatment outcomes

BEHAVIORAL MEDICINE STUDY SECTION

- ** R01DE-04004-07 Acupuncture and perception of dental pain (human)
- ** R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)
- ** R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)
- ** R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)
- ** R23DE-05799-01 Behavioral methods for pedodontic management (human)
- ** R23DE-05858-01 Dentists' behavior and treatment outcomes

BELL'S PALSY

SEE NERVOUS DISORDERS PERIPHERAL, FACIAL PARALYSIS

BENZANTHRACENES

SEE CYCLICS, CARBOPOLYCYCLICS, BENZANTHRACENES

BENZOPYRENES

SEE CYCLICS, CARBOPOLYCYCLICS, BENZOPYRENES

BENZOPYRROLE CARBOXYLIC ACIDS, INDOMETHACIN

- R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)
- R23DE-05393-03 Factors association with hyperplasia of oral mucosa
- R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)

BENZOPYRROLES, SEROTONIN

- P50DE-02668-15 0168 Regional dental research center - Thrombin-platelet interactions (human)
- R01DE-03469-10 Teratogens effects on cleft palate formation (mice)
- R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)
- R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)
- R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis (cats)
- R23DE-05605-01 The humoral regulation of pulp circulation (rats)

BETA RECEPTORS

SEE NEUROTRANSMITTERS RECEPTORS, ADRENERGIC RECEPTORS, BETA RECEPTORS

BEVERAGES

SEE FOOD, BEVERAGES

BINDING (CHEMICAL)

SEE CHEMICAL BONDS, BINDING

BINDING PROTEINS

SEE PROTEIN BINDING

BINDING REAGENTS

SEE METAL COMPLEXES, LIGANDS

BIOASSAY*

SEE ALSO CHEMICAL STRUCTURE-BIOLOGICAL ACTIVITY
SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOASSAY*

R01DE-05467-02 Pathogenesis of localized bone destruction

BIOAVAILABILITY OF DRUGS

SEE DRUGS, PHARMACOLOGY, BIOAVAILABILITY

BIOCHEMICAL PHARMACOLOGY

SEE DRUGS, PHARMACOLOGY, BIOCHEMICAL

BIOCHEMISTRY (GENERAL)*

SEE ALSO BIOCHEMISTRY STUDY SECTION
SEE ALSO HISTOCHEMISTRY AND CYTOCHEMISTRY (GENERAL)*
SEE ALSO IMMUNOCHEMISTRY

SEE ALSO MEDICINAL CHEMISTRY STUDY SECTION

SEE ALSO MOLECULAR BIOLOGY (GENERAL)

SEE ALSO NEUROCHEMISTRY

SEE ALSO PATHOBIOCHEMISTRY STUDY SECTION

SEE ALSO PHOTOCHEMISTRY

SEE ALSO PHYSIOLOGICAL CHEMISTRY STUDY SECTION

** P50DE-02668-15 0125 Regional dental research center - Collagen crosslinks and the fate of extracellular matrix

** P50DE-02668-15 0176 Regional dental research center - Collagen biochemistry and the myeloblastosis associated virus infected cells

** P50DE-02670-15 0025 Institute of Dental Research - Biochemical basis for the cariogenic property of Streptococcus mutants (rat)

R01DE-04385-06 Mechanism of dental caries (human)

R01DE-04857-02 Temporalis flaps in the treatment of facial paralysis (monkeys)

R23DE-05424-03 Quantitative studies of lysosomes in amelogenesis (rats)

** R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)

** R01DE-05684-01 Saliva proteins--Chemistry, genetics and oral health

BIOCHEMISTRY STUDY SECTION

** R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)

BIOCYBERNETICS (NEURAL)

SEE INFORMATION PROCESSING AND CONTROL (NEURAL)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

BIODEGRADATION, BIOTRANSFORMATION (METABOLISM)

SEE METABOLISM, BIOTRANSFORMATION

BIOELECTRICITY

SEE ELECTROPHYSIOLOGY

BIOENERGETICS

SEE ALSO BIOLOGICAL TRANSPORT
SEE ALSO OXIDATION-REDUCTION
SEE ALSO PHOTOCHEMISTRY
R01DE-05112-03 Muscle activity and control in mastication (mammals, lizards)

BIOENGINEERING

SEE BIOMEDICAL ENGINEERING
SEE SURGERY AND BIOENGINEERING STUDY SECTION

BIOEQUIVALENCE OF DRUGS

SEE DRUGS, PHARMACOLOGY, BIOAVAILABILITY

BIOFEEDBACK CONDITIONING (TRAINING)

SEE PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL CONTROL

BIOGENIC AMINES, NEURAL

SEE NEUROTRANSMITTERS AND NEUROMODULATORS (GENERAL)

BIOHAZARDS OF ORGANISMS OR THEIR PRODUCTS, AND THEIR CONTROL

SEE INJURY (HAZARDS) PREVENTION AND CONTROL, BIOHAZARDS (CONTROL)

BIOLOGICAL BASIS (CORRELATES) OF BEHAVIOR

SEE PSYCHOBIOLOGY, PSYCHOPHYSIOLOGY

BIOLOGICAL MODELS

SEE MODELS, BIOLOGICAL

BIOLOGICAL PREPARATIONS AND STANDARDIZATION

** R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
R01DE-04096-05 Biocompatibility of endodontic materials (animals)

BIOLOGICAL TRANSPORT

SEE ALSO CARBOHYDRATES TRANSPORT (GENERAL)
SEE ALSO PROTEINS TRANSPORT
R01DE-03780-09 Permeability characteristics of dentin (dogs, human)

BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT

SEE ALSO GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT (GENERAL)
SEE ALSO KIDNEY FUNCTION, RENAL TUBULAR TRANSPORT
R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS

SEE ALSO BIOLOGICAL TRANSPORT, ION EXCHANGE AND TRANSPORT, ION CARRIERS (IONOPHORES)
R01DE-04600-04 Hydroxypatite remineralization--Role of fluoride

BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS, CALCIUM PUMP

SEE ALSO NUTRITION, DIETARY CONSTITUENTS, DIETARY CALCIUM

P50DE-02623-14 0030 Center for oral health research - Role of mitochondria in the mineralization process (chickens)
P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel

** P50DE-02668-15 0193 Regional dental research center - Metabolism of isolated ameloblasts
P50DE-02668-15 0207 Regional dental research center - Effects of vitamin A and D, PTH, CT on uptake of calcium and phosphorus in enamel

P50DE-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins

R01DE-04897-02 Functional development of salivary glands (rats)

R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

** R01DE-05323-02 Calcium transport in developing dental tissues (frogs, rats)

R01DE-05510-02 Physico-chemistry of strontium in caries lesions

R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)

R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS, CHLORIDE PUMP

R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS, POTASSIUM PUMP

R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS, SODIUM PUMP

R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS, SODIUM-POTASSIUM PUMP

R01DE-04897-02 Functional development of salivary glands (rats)

R01DE-05586-01 Cell surface studies of the enamel organ (mice)

R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, PINOCYTOSIS

SEE ALSO CELL INGESTION, PHAGOCYTOSIS
R01DE-05251-02 Salivary gland secretory mechanisms (rats)
R01DE-05586-01 Cell surface studies of the enamel organ (mice)
R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

BIOLOGICAL TRANSPORT, ION EXCHANGE AND TRANSPORT

R01DE-01850-18 0087 Nutritional sources and metabolic roles of fluoride - Methodology for determining ionic fluoride content of human plasma

** R01DE-02110-17 Salivary gland structure and function (rats)

** P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel

P50DE-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology

P50DE-02668-15 0207 Regional dental research center - Effects of vitamin A and D, PTH, CT on uptake of calcium and phosphorus in enamel

P50DE-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins

** R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

R01DE-04385-06 Mechanism of dental caries (human)

R01DE-04600-04 Hydroxypatite remineralization--Role of fluoride

R01DE-04897-02 Functional development of salivary glands (rats)

** R01DE-04903-03 Trace metal uptake in cariogenic streptococcus mutans

R01DE-05596-02 Topically-applied polymers for caries prevention

R01DE-05652-01 Biological role of lysozyme in human saliva

R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

BIOLOGICAL TRANSPORT, ION EXCHANGE AND TRANSPORT, ION CARRIERS (IONOPHORES)

SEE ALSO ANTIBIOTICS, VALINOMYCIN
SEE ALSO PROTEINS, CALCIUM BINDING PROTEINS
P50DE-02623-14 0030 Center for oral health research - Role of mitochondria in the mineralization process (chickens)
R01DE-04897-02 Functional development of salivary glands (rats)
R01DE-05249-02 Salivary secretion-role of calcium (mice)
R01DE-05632-01 Development of salivary gland secretory function (rats)

BIOLOGICAL TRANSPORT, ION EXCHANGE AND TRANSPORT, ION CARRIERS (IONOPHORES)

SEE ALSO ANTIBIOTICS, VALINOMYCIN

SEE ALSO PROTEINS, CALCIUM BINDING PROTEINS

P50DE-02623-14 0030 Center for oral health research - Role of mitochondria in the mineralization process (chickens)

R01DE-04897-02 Functional development of salivary glands (rats)

R01DE-05249-02 Salivary secretion-role of calcium (mice)

R01DE-05632-01 Development of salivary gland secretory function (rats)

BIOLOGICAL TRANSPORT, MEMBRANE MODELS, LIPOSOMES

R01DE-03258-10 Streptococcus mutans--Dental caries mechanism (human)

BIOLOGICAL TRANSPORT, MEMBRANE PERMEABILITY AND TRANSPORT

SEE ALSO CARDIOVASCULAR SYSTEM, ENDOTHELIUM

PERMEABILITY

SEE ALSO GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT (GENERAL)

SEE ALSO KIDNEY FUNCTION, RENAL TUBULAR TRANSPORT

SEE ALSO MEMBRANE, MEMBRANE (BIOLOGICAL) STRUCTURE

SEE ALSO PREGNANCY CIRCULATION, PLACENTAL TRANSFER

P01DE-01850-18 0072 Nutritional sources and metabolic roles of fluoride - Effect of fluoride on iron transport (mice)

P01DE-01850-18 0085 Nutritional sources and metabolic roles of fluoride - Absorption of fluoride from dietary substances (rats)

R01DE-02110-17 Salivary gland structure and function (rats)

** P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel

P50DE-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology

P50DE-02668-15 0207 Regional dental research center - Effects of vitamin A and D, PTH, CT on uptake of calcium and phosphorus in enamel

** R01DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)

** R01DE-03780-09 Permeability characteristics of dentin (dogs, human)

R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)

R01DE-04385-06 Mechanism of dental caries (human)

R01DE-04897-02 Functional development of salivary glands (rats)

R01DE-04957-03 Bacterial metabolites in oral diseases
R01DE-05251-02 Salivary gland secretory mechanisms (rats)
R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

** R01DE-05525-02 Nature of the permeability barrier in oral epithelium

** R01DE-05586-01 Cell surface studies of the enamel organ (mice)

R01DE-05652-01 Biological role of lysozyme in human saliva

R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

R23DE-05887-01 Effects of oral bacteria on epithelium in vitro

BIOLOGICAL TRANSPORT, PASSIVE TRANSPORT

R01DE-01850-18 0072 Nutritional sources and metabolic roles of fluoride - Effect of fluoride on iron transport (mice)
R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

BIOLOGICAL TRANSPORT, PASSIVE TRANSPORT, DIFFUSION

R23DE-05155-02 Active principles of dental pulp therapeutic agents

R01DE-05156-03 Immunoidentification of periodontal plaque bacteria

BIOLOGICAL TRANSPORT, SECRETORY MECHANISMS

SEE ALSO ORAL-PHARYNGEAL, SALIVATION

** R01DE-02110-17 Salivary gland structure and function (rats)

P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)

** P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction

** P50DE-02623-14 0026 Center for oral health research - Collagen biosynthesis in the periodontium

P50DE-02623-14 0027 Center for oral health research - Collagenase in the periodontium

P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel

** P50DE-02668-15 0192 Regional dental research center - Skeletal actions of calcitonin in the rat

P50DE-02668-15 0193 Regional dental research center - Metabolism of isolated ameloblasts

** P50DE-02670-15 0018 Institute of Dental Research - Structure of human secretory immunoglobulin A

** P50DE-02670-15 0037 Institute of Dental Research - Cellular basis of induction of secretory immune response (mice)

R01DE-03666-07 X-ray therapeutic index for salivary glands

R01DE-04230-07 Comparative ultrastructure of mammalian amelogenesis (human, mammals)

R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism

** R01DE-04897-02 Functional development of salivary glands (rats)

R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)

R23DE-05142-03 Control mechanisms in salivary gland development (rats)

R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)

** R01DE-05249-02 Salivary secretion-role of calcium (mice)

** R01DE-05251-02 Salivary gland secretory mechanisms (rats)

** R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

R23DE-05424-03 Quantitative studies of lysosomes in amelogenesis (rats)

R01DE-05531-03 Salivary immune factors (human, bacteria)

R01DE-05586-01 Cell surface studies of the enamel organ (mice)

** R01DE-05632-01 Development of salivary gland secretory function (rats)

R01DE-05652-01 Biological role of lysozyme in human saliva

R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

R23DE-05749-01 Salivary proline-rich proteins--Localization/secretion (monkeys)

R01DE-05773-01 Ligand receptor interactions of cariogenic bacteria

R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)

R23DE-05985-01 Growth factors in salivary secretions

R01DE-06000-01 Effect of parotid function on saliva and cells

BIOLOGICAL TRANSPORT, SECRETORY MECHANISMS, EXCRETION

** P01DE-01850-18 0075 Nutritional sources and metabolic roles of fluoride - Metabolic handling of perfluorooctanoic acid (rats)

BIOLOGICAL TRANSPORT, TRANSPORT EFFECTORS

SEE ALSO BIOLOGICAL TRANSPORT, ION EXCHANGE AND TRANSPORT, ION CARRIERS (IONOPHORES)

SEE ALSO BIOLOGICAL TRANSPORT, TRANSPORT PROTEINS

(SEE ALSO SPECIFICS)

P50DE-02623-14 0030 Center for oral health research - Role of mitochondria in the mineralization process (chickens)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

- R01DE-05525-02 Nature of the permeability barrier in oral epithelium
 R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

BIOLOGICAL TRANSPORT, TRANSPORT

PROTEINS (SEE ALSO SPECIFICS)

- SEE ALSO ENDOCRINOLOGY, HORMONE BINDING PROTEINS
 SEE ALSO METALLOPROTEINS, TRANSFERRIN
 SEE ALSO PROTEIN BINDING
 SEE ALSO PROTEINS, CALCIUM BINDING PROTEINS
 P50DE-02623-14 0030 Center for oral health research - Role of mitochondria in the mineralization process (chickens)
 R01DE-03258-10 Streptococcus mutans-Dental caries mechanism (human)

BIOLOGICAL RESOURCES

- SEE BIOLOGICAL PREPARATIONS AND STANDARDIZATION

BIOLOGY, POLYMORPHISM

- ** R01DE-03658-17 Genetic polymorphisms of saliva (human)

BIOLOGY, SYSTEMATIC

- SEE ALSO MICROBIAL IDENTIFICATION AND CLASSIFICATION (TECHNIQUES)

- ** R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)

BIOLOGY, SYSTEMATIC, GENETIC STRAINS

- R01DE-01850-18 0081 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on strain N mice
 ** P50DE-02668-15 0213 Regional dental research center - Hormone action is the salivary glands of inbred mice
 R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)
 R01DE-04645-04 A genetic-biochemical analysis of spirochete motility
 R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)
 R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)
 R01DE-05168-03 Glucocorticoid receptors and cleft palate (mice)
 R01DE-05218-03 DNA homologies among bacteria of periodontal diseases
 ** R01DE-05367-02 Cranio-facial anomalies in the oel mouse
 R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)
 R01DE-05459-02 Phenytoin-Pathogenesis of gingival overgrowth (cats)
 R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)
 R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)

BIOLOGY, SYSTEMATIC, SPECIES

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
 ** R23DE-05491-02 Control of biomineralization in two species (snails)

BIOMATERIALS

- SEE ALSO DENTAL MATERIALS

- SEE ALSO ORAL-FACIAL RESTORATION MATERIALS

- SEE ALSO SKELETAL DISORDERS, ORTHOTIC MATERIALS

- SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT, IMPLANT

- ** R01DE-04096-05 Biocompatibility of endodontic materials (animals)
 ** R13DE-05898-01 13th Annual International Biomaterials Symposium - 1981

BIOMATERIALS, BIOMATERIALS EVALUATION

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
 ** R01DE-04252-07 Semi and nonprecious metal-porcelain systems
 ** R01DE-05292-03 Biological prosthetic attachment (dog)
 ** R01DE-05637-01 Mechanical properties of dental composite materials
 R23DE-05945-01 Physicochemical modifications of dental restoratives
 R01DE-06112-01 Filled sealant as a conservative restorative material (human)

BIOMATERIALS, DEVELOPMENT AND PREPARATION OF BIOMATERIALS

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
 ** R01DE-04136-07 Maxillofacial materials-Color study
 R01DE-05637-01 Mechanical properties of dental composite materials
 R01DE-06112-01 Filled sealant as a conservative restorative material (human)

BIOMATERIALS, INTERFACIAL PHENOMENA

- SEE ALSO MEMBRANE SURFACE (BIOLOGICAL) ACTIVITY (GENERAL)

- SEE ALSO PHYSICAL PROPERTIES, SURFACE PROPERTIES (GENERAL)

- ** R01DE-05292-03 Biological prosthetic attachment (dog)

BIOMATERIALS EVALUATION

- SEE BIOMATERIALS, BIOMATERIALS EVALUATION

BIOMATERIALS DESIGN

- SEE BIOMATERIALS, DEVELOPMENT AND PREPARATION OF BIOMATERIALS

BIOMATERIAL-TISSUE SURFACE INTERACTIONS

- SEE BIOMATERIALS, INTERFACIAL PHENOMENA

BIOMECHANICS

- SEE BIOPHYSICS, BIOMECHANICS

BIOMEDICAL DATA COMPUTER PROCESSING

- SEE BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER PROCESSING OF LABORATORY DATA (GENERAL)

BIOMEDICAL ENGINEERING

- SEE ALSO BIOPHYSICS (GENERAL)*

- SEE ALSO SURGERY AND BIOENGINEERING STUDY SECTION

- P50DE-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)
 R01DE-03953-07 Force systems from orthodontic appliances
 R01DE-05321-02 Titanium alloys in dentistry
 ** R13DE-05468-01 Symposium on orthodontics and bioengineering (Connecticut)

BIOMEDICAL ENGINEERING, INSTRUMENTATION CLINICALLY ORIENTED

- R01DE-03631-08 Physiological study of speech adaptation (human)
 R01DE-04157-08 Functional mandibular movements (human)
 ** R01DE-04783-04 The development of a dental x-ray aiming device
 R01DE-04990-03 Normal and abnormal faces (human)
 R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
 R23DE-05527-02 Behavioral treatments for nocturnal bruxism (human)
 R01DE-05560-01 Rapid identification of oral bacteria
 ** R01DE-05761-02 Improved dental instruments and materials

BIOMEDICAL ENGINEERING, MEDICAL

EQUIPMENT SAFETY

- R23DE-05507-02 Psychomotor impairment related to N20 exposure (human)

BIOMEDICAL FACILITIES

- SEE ALSO BIOMEDICAL SYSTEMS AUTOMATED

- ** P50DE-02600-15 9001 Support for oral biology research center - Core
 ** P01DE-02872-12 9001 Craniofacial dysmorphology - Core

BIOMEDICAL LIBRARY REVIEW COMMITTEE

- SEE LIBRARY (BIOMEDICAL) REVIEW COMMITTEE

BIOMEDICAL RESEARCH

- SEE HEALTH SCIENCES RESEARCH (GENERAL)*

BIOMEDICAL SYSTEMS AUTOMATED

- SEE ALSO OPTICS, IMAGE PROCESSING ANALYSIS AND DISPLAY*

- P01DE-02872-12 9001 Craniofacial dysmorphology -

BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER ASSISTED DIAGNOSIS

- R01DE-03598-07 Dentofacial effects of forces to retract the maxilla (human)
 R01DE-04157-08 Functional mandibular movements (human)
 R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)

BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER ASSISTED MEDICAL DECISION MAKING

- SEE ALSO BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER ASSISTED DIAGNOSIS
 ** R01DE-04990-03 Normal and abnormal faces (human)

BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER PROCESSING OF CLINICAL DATA

- SEE ALSO BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER ASSISTED DIAGNOSIS
 SEE ALSO BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER ASSISTED MEDICAL DECISION MAKING

- ** P01DE-02872-12 0018 Craniofacial dysmorphology - Data bank-Computerization of clinical data
 P01DE-02872-12 0034 Craniofacial dysmorphology - Digitization of roentgencephalometric data (human)
 ** P01DE-02872-12 0056 Craniofacial dysmorphology - Center for craniofacial anomalies
 P01DE-02872-12 0062 Craniofacial dysmorphology - Congenital palatopharyngeal incompetence
 R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)

BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER PROCESSING OF LABORATORY DATA (GENERAL)

- M P50DE-02600-15 Support for oral biology research center
 M P01DE-02623-14 Center for oral health research
 P50DE-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)
 R01DE-03703-05 Integrated three-dimensional craniofacial measurement (human)
 R01DE-04600-04 Hydroxyapatite remineralization--Role of fluoride

BIOMEDICAL SYSTEMS AUTOMATED, HEALTH CARE FACILITIES (SYSTEMS) INFORMATION SYSTEMS

- SEE ALSO HEALTH RECORDS (SYSTEMS) AUTOMATED

- ** P01DE-02872-12 0018 Craniofacial dysmorphology - Data bank-Computerization of clinical data

BIOMEDICAL SYSTEMS AUTOMATED, MONITORING DEVICES

- ** R01DE-04783-04 The development of a dental x-ray aiming device

BIOMETRY

- SEE MATHEMATICS, STATISTICS (INCLUDING BIOMETRY)

BIONOMICS

- SEE PSYCHOLOGY, BEHAVIOR ANIMAL

BIOPERIODICITY, CIRCADIAN RHYTHMS

- R01DE-06113-01 Determinants of fluoride in the oral environment (Dogs, rats)

BIOPHYSICS (GENERAL)*

- SEE ALSO BIOMEDICAL ENGINEERING
 R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

BIOPHYSICS, BIOMECHANICS

- R01DE-04990-03 Normal and abnormal faces (human)
 R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
 ** R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
 R01DE-05292-03 Biological prosthetic attachment (dog)
 R23DE-05314-03 Dental alloy corrosion research
 R01DE-05321-02 Titanium alloys in dentistry
 R23DE-05418-03 In vivo forces on endosseous dental implants (dogs)

BIO-PSYCHOLOGY STUDY SECTION

- ** R01DE-04786-04 Dental and orofacial pain-Brain stem mechanisms (cats)
 ** R01DE-05204-03 Operant neural control in trigeminal pain systems (rat)

BIOSTATISTICS

- SEE MATHEMATICS, STATISTICS (INCLUDING BIOMETRY)

BIOSYNTHESIS OF CARBOHYDRATES

- SEE CARBOHYDRATES BIOSYNTHESIS

BIOSYNTHESIS OF HORMONES

- SEE ENDOCRINOLOGY, HORMONES BIOSYNTHESIS

BIOSYNTHESIS OF IMMUNOGLOBULIN

- SEE GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN BIOSYNTHESIS

BIOSYNTHESIS OF NEUROTRANSMITTERS

- SEE NEUROTRANSMITTERS BIOSYNTHESIS

BIOSYNTHESIS OF PROTEINS

- SEE PROTEINS BIOSYNTHESIS

BIOTRANSFORMATION (METABOLISM)

- SEE METABOLISM, BIOTRANSFORMATION

BIRTH ORDER

- SEE FAMILY, SIBLING ORDER

BIRTH WEIGHT (HUMAN)

- SEE CHILDREN, INFANT PREMATURE AND LOW BIRTH WEIGHT

BITE

- SEE DENTAL OCCLUSION, BITE AND BITING STRENGTH (FORCE)

BITING STRENGTH (FORCE)

- SEE DENTAL OCCLUSION, BITE AND BITING STRENGTH (FORCE)

BIVALVES

- SEE MOLLUSKS, PELECYPODS*

BLACK AMERICANS

- SEE SOCIAL GROUPS, ETHNIC, AMERICANS, BLACK AMERICANS

BLASTODERM

- SEE EMBRYOLOGY, GERM LAYERS

BLEPHARITIS

- SEE EYE DISORDERS, EYELID DISORDERS

BLOOD

- SEE BLOOD AND RE SYSTEM, BLOOD*

BLOOD AND RE DISORDERS, LEUKOCYTE DISORDERS, LEUKOPENIA

- ** P50DE-02670-15 0035 Institute of Dental Research - Granulocyte growth and division

BLOOD AND RE SYSTEM, BLOOD*

- SEE ALSO BLOOD AND RE SYSTEM, HEMATOPOIESIS

- SEE ALSO BLOOD CELLS

- SEE ALSO BLOOD PROTEINS

- SEE ALSO CARDIOVASCULAR FUNCTION, BLOOD CIRCULATION DYNAMICS (GENERAL)

- N01DE-12430-00 Investigation of anticaries vaccine in primates

BLOOD AND RE SYSTEM, BLOOD, PLASMA

- ** P01DE-01850-18 0087 Nutritional sources and metabolic roles of fluoride - Methodology for determining ionic fluoride content of human plasma

BLOOD AND RE SYSTEM, BLOOD, SERUM

- SEE ALSO IMMUNOLOGY, ANTIBODIES, IMMUNE SERA
 SEE ALSO IMMUNOLOGY, SEROLOGY*

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects
 See Appendix for investigator's name and Grant Number

(contd).

- P01DE-01850-18 0082 Nutritional sources and metabolic roles of fluoride - Nonionic fluoride in foods (human)
- ** P01DE-01850-18 0086 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on serum alkaline phosphatase activity (mice)
- R23DE-05429-03 Adherence of periodontal disease-associated bacteria
- R01DE-05758-01 Genetic linkage study of cleft lip-palate in Denmark

BLOOD AND RE SYSTEM, BONE MARROW TRANSPLANTATION

- R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)

BLOOD AND RE SYSTEM, HEMATOPOIESIS

- R01DE-06065-01 The role of lymphoid cells in alveolar bone resorption

BLOOD AND RE SYSTEM, LYMPHATIC TISSUE

- SEE ALSO BLOOD AND RE SYSTEM, SPLEEN
SEE ALSO BLOOD AND RE SYSTEM, THYMUS
- R01DE-05467-02 Pathogenesis of localized bone destruction
- ** R01DE-06065-01 The role of lymphoid cells in alveolar bone resorption

BLOOD AND RE SYSTEM, LYMPHATIC TISSUE, LYMPH NODES

- R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)

BLOOD AND RE SYSTEM, MACROPHAGES

- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- P50DE-02623-14 0023 Center for oral health research - Interactions of oral bacteria and polymorphonuclear leukocytes
- P50DE-02623-14 0027 Center for oral health research - Collagenase in the periodontium
- P50DE-02623-14 0033 Center for oral health research - Immune system in regulation of angiogenesis
- ** P50DE-02731-15 0035 Development support for dental research institute - Immune regulation in periodontal disease
- R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)
- R01DE-04217-07 Effective immunity to dental caries--Cellular basis
- R01DE-04808-02 Virulence factors of gram negative corroding bacteria
- R01DE-04844-04 Stress-related bone resorption--Mechanisms of action (rats)
- R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
- R23DE-05050-02 Sources of toxins from human dental plaque
- R23DE-05117-03 Enhancement of oral cancer after allografting (mice)
- R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)
- R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
- ** R01DE-05413-02 Bone resorption in periodontal disease
- ** R01DE-05494-02 Activation of macrophages in periodontal disease
- ** R01DE-05512-02 Role of macrophages in periodontal disease
- R01DE-05626-01 Role of complement in periodontal disease
- BLOOD AND RE SYSTEM, MEGAKARYOCYTES**
- R01DE-05109-02 Composite bone grafts in dentistry and medicine

BLOOD AND RE SYSTEM, SPLEEN

- R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)

BLOOD AND RE SYSTEM, THYMUS

- R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)

BLOOD BACTERICIDAL ACTIVITY (GENERAL)

SEE IMMUNITY, BACTERICIDAL DEFENSES (GENERAL)

BLOOD CELL FORMATION

SEE BLOOD AND RE SYSTEM, HEMATOPOIESIS

BLOOD CELLS

- R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)

BLOOD CELLS, ERYTHROCYTES

- R01DE-05758-01 Genetic linkage study of cleft lip-palate in Denmark

BLOOD CELLS, LEUKOCYTES

- SEE ALSO BLOOD CELLS, LYMPHOCYTES
SEE ALSO BLOOD CELLS, MONOCYTES
SEE ALSO CELL INGESTION, PHAGOCYTOSIS
- ** P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)
- R01DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)
- R01DE-05758-01 Genetic linkage study of cleft lip-palate in Denmark
- R23DE-05789-01 IgA receptor bearing oral cells in cystic fibrosis (human)

BLOOD CELLS, LEUKOCYTES, GRANULOCYTES (GENERAL)

- ** P50DE-02670-15 0035 Institute of Dental Research - Granulocyte growth and division

BLOOD CELLS, LEUKOCYTES, NEUTROPHILS

- ** P50DE-02600-15 0030 Support for oral biology research center - Leukocyte function--Its role in periodontal disease (human)
- P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)
- ** P50DE-02623-14 0023 Center for oral health research - Interactions of oral bacteria and polymorphonuclear leukocytes
- P50DE-02623-14 0027 Center for oral health research - Collagenase in the periodontium
- P50DE-02623-14 0032 Center for oral health research - Interactions of salivary agglutinins and oral bacteria
- R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)
- R01DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)
- ** R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)
- R01DE-04808-02 Virulence factors of gram negative corroding bacteria
- P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)
- P50DE-05139-04 0003 Clinical research center for periodontal disease - Polymorphonuclear leukocyte functions
- ** R23DE-05331-01 Local host mechanism in periodontal disease (human, monkeys)
- R01DE-05494-02 Activation of macrophages in periodontal disease
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05640-01 Cytotoxicity of periodontopathic bacteria

BLOOD CELLS, LYMPHOCYTES

- ** P50DE-02731-15 0035 Development support for dental research institute - Immune regulation in periodontal disease
- R01DE-04296-07 Lysozyme-Cell surface interactions and oral defense
- R23DE-05050-02 Sources of toxins from human dental plaque
- R01DE-05322-01 Genetic analysis of birth defects involving septa (human, mice)

BLOOD CELLS, LYMPHOCYTES, KILLER CELLS

- R01DE-05414-02 The local immune response in periodontal disease (human)

BLOOD CELLS, B LYMPHOCYTES

- SEE ALSO IMMUNOGENETICS, HISTOCOMPATIBILITY GENES
- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
- P50DE-02623-14 0033 Center for oral health research - Immune system in regulation of angiogenesis
- P50DE-02670-15 0018 Institute of Dental Research - Structure of human secretory immunoglobulin A
- P50DE-02670-15 0037 Institute of Dental Research - Development support for dental research institute - Immune regulation in periodontal disease
- R01DE-03420-09 Immune phenomena in experimental periodontal disease (rats)
- R01DE-04217-07 Effective immunity to dental caries--Cellular basis
- P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
- P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations
- R01DE-05414-02 The local immune response in periodontal disease (human)
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05626-01 Role of complement in periodontal disease
- R01DE-05732-02 Specificity of cell mediated immune response in periodontal disease

BLOOD CELLS, T LYMPHOCYTES

- SEE ALSO IMMUNOGENETICS, HISTOCOMPATIBILITY GENES
- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
- P50DE-02623-14 0033 Center for oral health research - Immune system in regulation of angiogenesis
- P50DE-02670-15 0018 Institute of Dental Research - Structure of human secretory immunoglobulin A
- P50DE-02670-15 0037 Institute of Dental Research - Development support for dental research institute - Immune regulation in periodontal disease
- R01DE-03420-09 Immune phenomena in experimental periodontal disease (rats)
- R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)
- R01DE-04217-07 Effective immunity to dental caries--Cellular basis
- R01DE-04501-06 Cell mediated immunity in gingival inflammation (mice)

- P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05626-01 Role of complement in periodontal disease
- R01DE-05732-02 Specificity of cell mediated immune response in periodontal disease

BLOOD CELLS, T LYMPHOCYTES, SUPPRESSOR

- R23DE-05117-03 Enhancement of oral cancer after allografting (mice)

BLOOD CELLS, MONOCYTES

- ** P50DE-02600-15 0030 Support for oral biology research center - Leukocyte function--Its role in periodontal disease (human)
- P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)
- R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)
- R01DE-04217-07 Effective immunity to dental caries--Cellular basis
- R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)
- R01DE-05413-02 Bone resorption in periodontal disease
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- ** R01DE-05512-02 Role of macrophages in periodontal disease
- R01DE-05732-02 Specificity of cell mediated immune response in periodontal disease

BLOOD CHEMISTRY

SEE CHEMISTRY, CLINICAL, BLOOD

BLOOD CIRCULATION DYNAMICS

SEE CARDIOVASCULAR FUNCTION, BLOOD CIRCULATION DYNAMICS (GENERAL)

BLOOD CIRCULATORY SYSTEMS

SEE SKELETAL SYSTEM CIRCULATION

BLOOD COAGULATION, ANTITHROMBINS

- ** P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin

BLOOD COAGULATION, FACTOR X

- P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin

BLOOD COAGULATION, FIBRINOGEN

- P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin

BLOOD COAGULATION, PROTHROMBIN

- P50DE-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology
- P50DE-02668-15 0168 Regional dental research center - Thrombin-platelet interactions (human)
- ** P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin

BLOOD COAGULATION, THROMBIN

- ** P50DE-02668-15 0168 Regional dental research center - Thrombin-platelet interactions (human)
- ** P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin

BLOOD FLOW

SEE CARDIOVASCULAR FUNCTION, BLOOD FLOW

BLOOD PLATELETS

- SEE ALSO BLOOD AND RE SYSTEM, MEGAKARYOCYTES
- ** P50DE-02668-15 0168 Regional dental research center - Thrombin-platelet interactions (human)
- P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin
- ** R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)

BLOOD PLATELETS, PLATELET ACTIVATING FACTOR

- P50DE-02668-15 0168 Regional dental research center - Thrombin-platelet interactions (human)

BLOOD PLATELETS DEFECTS QUALITATIVE

SEE BLOOD PLATELETS DISORDERS, THROMBOCYTOPATHY

BLOOD PLATELETS DISORDERS, THROMBOCYTOPATHY

- P50DE-02668-15 0168 Regional dental research center - Thrombin-platelet interactions (human)

BLOOD PRESSURE

SEE CARDIOVASCULAR FUNCTION, BLOOD PRESSURE

BLOOD PROTEINS

- SEE ALSO IMMUNOLOGY, COMPLEMENT
SEE ALSO METALLOPROTEINS, TRANSFERRIN
- R01DE-01554-20 Host factors in caries resistance (human, rats)
- P01DE-01850-18 0075 Nutritional sources and metabolic roles of fluoride - Metabolic handling of perfluorooctanoic acid (rats)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M. Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

BLOOD STASIS

- ** P50DE-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology
- P50DE-02668-15 0168 Regional dental research center - Thrombin-platelet interactions (human)
- P50DE-02668-15 0130 Regional dental research center - Thrombin and prothrombin

BLOOD SUPPLY

SEE CARDIOVASCULAR SYSTEM, BLOOD SUPPLY

BLOOD VESSELS

SEE CARDIOVASCULAR SYSTEM, BLOOD VESSELS (GENERAL)

BLOOD VESSELS DISORDERS (GENERAL)

SEE CARDIOVASCULAR DISORDERS, VASCULAR DISORDERS (GENERAL)

BODY CAVITY DISORDERS, PERITONEAL

M P50DE-02670-15 Institute of Dental Research

BODY FLUIDS (AND RELATED SUBSTANCES)

- SEE ALSO BLOOD AND RE SYSTEM, BLOOD*
- SEE ALSO BODY FLUID BALANCE, BODY WATER
- SEE ALSO ORAL-PHARYNGEAL, SALIVA
- SEE ALSO SKELETAL SYSTEM, SYNOVIAL FLUID
- SEE ALSO URINE*
- R01DE-01554-20 Host factors in caries resistance (human, rats)

BODY FLUIDS, EXTRACELLULAR SPACE (COMPARTMENT)

- ** R01DE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)
- ** R01DE-05483-02 Characterization of predentinal extracellular fluid (rats)

BODY FLUIDS, MILK

- SEE ALSO NUTRIENT INTAKE ACTIVITY, BREAST FEEDING
- P01DE-01850-18 0085 Nutritional sources and metabolic roles of fluoride - Absorption of fluoride from dietary substances (rats)
- R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

BODY FLUID BALANCE, ACID-BASE

- SEE ALSO ACIDS-BASES, HYDROGEN-ION CONCENTRATION
- SEE ALSO URINE ACIDITY
- R01DE-03993-07 Effect of saliva on the metabolism of dental plaque
- ** R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

BODY FLUID BALANCE, BODY WATER

- R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)

BODY FLUID BALANCE, EDEMA

- R23DE-05967-01 Role of prostaglandin E in periodontal disease activity

BODY FLUID BALANCE, OSMOTIC PRESSURE

- R01DE-03780-09 Permeability characteristics of dentin (dogs, human)

BODY IMAGE

SEE SENSORY-PERCEPTUAL PROCESSES, BODY IMAGE

BODY MOVEMENT

SEE SKELETAL MOVEMENT, BODY MOVEMENT

BODY MOVEMENT SENSE

SEE SENSORY-PERCEPTUAL PROCESSES, PROPRIOCEPTION

BODY PHYSICAL CHARACTERISTICS (GENERAL)

- SEE ALSO SKELETAL DISORDERS DIAGNOSIS (INCL EXAMS)*
- R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
- M P01DE-03610-15 Cranio-facial growth and development
- ** R01DE-04990-03 Normal and abnormal faces (human)

BODY PHYSICAL CHARACTERISTICS, CEPHALOMETRY

- P01DE-02872-12 0018 Craniofacial dysmorphology - Date bank--Computerization of clinical data
- P01DE-02872-12 0063 Craniofacial dysmorphology - Premature craniofacial synostoses (human)
- R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
- ** P01DE-03568-07 0009 Craniofacial anomalies--Etiology and treatment - Cephalometrics
- ** R01DE-03703-05 Integrated three-dimensional craniofacial measurement (human)
- R01DE-05078-05 Craniofacial growth and remodeling (human)
- R01DE-05410-02 Orthodontic treatment effects on craniofacial growth (human)
- ** R01DE-05582-01 Computer graphic analysis of cranio-facial morphology

BODY POSITION SENSE

SEE SENSORY-PERCEPTUAL PROCESSES, PROPRIOCEPTION

BODY REGIONS, HEAD

- SEE ALSO BODY PHYSICAL CHARACTERISTICS, CEPHALOMETRY
- SEE ALSO NEOPLASMS OF BODY REGIONS, HEAD AND NECK
- SEE ALSO SKELETAL MOVEMENT, HEAD MOVEMENT
- SEE ALSO SKELETAL SYSTEM, SKULL

- R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)
- ** R01DE-05078-05 Craniofacial growth and remodeling (human)
- R01DE-05215-03 Influences on stability following orthognathic surgery
- ** R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)

BODY REGIONS, HEAD, FACE

- SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL
- SEE ALSO NASAL, NOSE
- SEE ALSO ORAL-FACIAL RESTORATION
- SEE ALSO ORAL-PHARYNGEAL, CHEEK
- R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)
- ** P50DE-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)
- ** P50DE-02668-15 0196 Regional dental research center - Cytochemical demonstration of macromolecules of craniofacial tissue
- ** P50DE-02668-15 0197 Regional dental research center - Peripheral nerves of the orofacial region
- ** R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)

- M P01DE-03610-15 Cranio-facial growth and development
- ** P01DE-03610-15 0016 Cranio-facial growth and development - Craniofacial shape change and oral development
- ** R01DE-03703-05 Integrated three-dimensional craniofacial measurement (human)
- ** R01DE-03715-06 Cellular assembly--Its role in facial morphogenesis (fungi)
- ** R01DE-04531-04 Strain in the facial bones of (primates)
- ** R01DE-04990-03 Normal and abnormal faces (human)
- R01DE-05138-03 Visceral arches and oro-facial morphogenesis (mice, monkeys)
- ** R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
- R23DE-05232-03 Growth and function of the muscles of mastication (monkeys)
- ** R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)
- R01DE-05728-01 Role of chemoreceptors in craniofacial function (lambs)

BODY REGIONS, NECK

- SEE ALSO NEOPLASMS OF BODY REGIONS, HEAD AND NECK
- R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

BODY SENSE

SEE SENSORY-PERCEPTUAL PROCESSES, SOMESTHESIS

BODY TEMPERATURE

SEE TEMPERATURE (BODY)

BODY TEMPERATURE REGULATION

SEE TEMPERATURE (BODY) REGULATION

BODY WATER BALANCE

SEE BODY FLUID BALANCE, BODY WATER

BOND FORMATION

SEE CHEMICAL BONDS, BOND FORMATION

BONDING

SEE DENTAL MATERIALS, BONDING

BONDS

SEE CHEMICAL BONDS

BONE

SEE SKELETAL SYSTEM, BONE

BONE AND CARTILAGE CONGENITAL ABNORMALITIES

SEE CONGENITAL ABNORMALITIES, SKELETAL (GENERAL)

BONE BANK

SEE SKELETAL TISSUE PRESERVATION, BONE

BONE CELLS

SEE SKELETAL SYSTEM, BONE CELLS

BONE CIRCULATION

SEE SKELETAL SYSTEM CIRCULATION

BONE DEVELOPMENT

SEE SKELETAL SYSTEM, BONE DEVELOPMENT

BONE DEVELOPMENT DISORDERS

SEE SKELETAL DISORDERS, BONE DEVELOPMENT

BONE DEVELOPMENT DISORDERS CONGENITAL

SEE CONGENITAL ABNORMALITIES, SKELETAL (GENERAL)

BONE DISORDERS

SEE SKELETAL DISORDERS, BONE DISORDERS (GENERAL)

BONE DISORDERS, METABOLIC (GENERAL)

SEE SKELETAL DISORDERS, BONE METABOLISM (GENERAL)

BONE FRACTURES

SEE INJURIES, FRACTURES

BONE MARROW GIANT CELLS

SEE BLOOD AND RE SYSTEM, MEGAKARYOCYTES

BONE MARROW LYMPHOCYTES

SEE BLOOD CELLS, B LYMPHOCYTES

BONE MARROW TRANSPLANTATION

SEE BLOOD AND RE SYSTEM, BONE MARROW TRANSPLANTATION

BONE METABOLISM DISORDERS (GENERAL)

SEE SKELETAL DISORDERS, BONE METABOLISM (GENERAL)

BONE MINERALIZATION

SEE SKELETAL SYSTEM, BONE DEVELOPMENT, OSSIFICATION

NDRMAL

BONE NEOPLASMS

SEE NEOPLASMS OF SKELETAL SYSTEM, BONE NEOPLASMS

BONE PRESERVATION

SEE SKELETAL TISSUE PRESERVATION, BONE

BONE PROSTHESIS

SEE SKELETAL TISSUE PROSTHESIS, BONE

BONE REGENERATION

SEE SKELETAL SYSTEM REGENERATION, BONE REGENERATION

BONE RESORPTION, TEETH

SEE DENTAL DISORDERS, TOOTH RESORPTION

BONE RESORPTION ABNORMAL

SEE SKELETAL DISORDERS, BONE RESORPTION ABNORMAL

BONE RESORPTION-REMODELING

PHYSIOLOGIC
SEE SKELETAL SYSTEM, BONE RESORPTION-REMODELING
PHYSIOLOGIC

BONE STRESS

SEE SKELETAL STRESS

BONE TRANSPLANTATION

SEE SKELETAL TISSUE TRANSPLANTATION, BONE

BRADYKININ

SEE PEPTIDES, VASOACTIVE PEPTIDES, KALLIDIN-9

BRAIN, AUDITORY PATHWAYS

- P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

BRAIN, BRAIN STEM

- ** R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)
- R23DE-05310-03 Neural control of mandibular movement
- R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis (cats)
- R01DE-05728-01 Role of chemoreceptors in craniofacial function (lambs)

BRAIN, CEREBRAL CORTEX

- SEE ALSO BRAIN ELECTRICAL ACTIVITY
- P50DE-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli
- R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis (cats)

BRAIN, CEREBRAL CORTEX, MOTOR CORTEX

- R23DE-05310-03 Neural control of mandibular movement

BRAIN, CEREBRAL CORTEX, SOMESTHETIC

SENSORY AREA
SEE ALSO NERVOUS SYSTEM, AFFERENT NERVES, CUTANEOUS SENSORY NERVES

- ** P50DE-02668-15 0199 Regional dental research center - Mechanisms governing the behavior of somatosensory cerebral cortical neurons
- ** P50DE-02668-15 0200 Regional dental research center - Response of first order mechanoreceptive afferents to moving tactile stimuli
- ** P50DE-02668-15 0210 Regional dental research center - Somesthetic capacities of human subjects (monkeys)
- R01DE-04884-13 Neural processes in somatic movement (monkeys)
- R01DE-05204-03 Operant neural control in trigeminal pain systems (rat)

BRAIN, MESENCEPHALON

- R01DE-05159-03 Distribution and ultrastructure of dental innervation (cats, rats)
- ** R01DE-05832-01 Organization of the trigeminal mesencephalic nucleus (monkeys, opossums)

BRAIN, MESENCEPHALON, RAPHE NUCLEUS, DORSAL

- R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis (cats)

BRAIN, PONS, TRIGEMINAL NUCLEUS (SPINAL)

- R01DE-05204-03 Operant neural control in trigeminal pain systems (rat)
- ** R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis (cats)

- ** R01DE-05832-01 Organization of the trigeminal mesencephalic nucleus (monkeys, opossums)

BRAIN, PROSENCEPHALON (GENERAL)

- R01DE-04884-13 Neural processes in somatic movement (monkeys)

BRAIN, THALAMUS

- R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis (cats)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

BRAIN APLASIA

SEE CONGENITAL ABNORMALITIES, BRAIN, ANENCEPHALUS

BRAIN DISORDERSSEE ALSO NERVOUS DISORDERS CENTRAL, ENCEPHALITIS
SEE ALSO SENSORY/PERCEPTUAL DISORDERS, SENSORY DISORDERS

R23DE-05310-03 Neural control of mandibular movement

BRAIN DISORDERS, EPILEPSY

R01DE-05459-02 Phenyltoin-Pathogenesis of gingival overgrowth (cats)

BRAIN ELECTRICAL ACTIVITY

SEE ALSO BRAIN DISORDERS, EPILEPSY

R01DE-04004-07 Acupuncture and perception of dental pain (human)

P01DE-05130-03 0006 Dental/orofacial pain-Mechanisms behavior and modulation - Acute pain in research and clinical settings

BRAIN OSCILLOGRAPHY

SEE BRAIN ELECTRICAL ACTIVITY

BRAIN STEM

SEE BRAIN, BRAIN STEM

BRAIN VISUALIZATION, ENCEPHALOGRAPHY*

- ** P01DE-02872-12 0034 Craniofacial dysmorphology - Digitization of roentgencephalometric data (human)
- P01DE-02872-12 0058 Craniofacial dysmorphology - Ophthalmology (human, rabbits)
- P01DE-02872-12 0063 Craniofacial dysmorphology - Premature craniofacial synostoses (human)

BREAST FEEDING

SEE NUTRIENT INTAKE ACTIVITY, BREAST FEEDING

BREATHING

SEE RESPIRATORY FUNCTION, RESPIRATION

BRITTLE DIABETES

SEE CARBOHYDRATES METABOLISM DISORDERS, DIABETES, INSULIN-DEPENDENT DIABETES

5-BROMODEOXYURIDINE

SEE HALOPYRIMIDINE NUCLEOSIDES, HALOURACIL NUCLEOSIDES, 5-BROMODEOXYURIDINE

BRONCHIAL ASTHMA

SEE HYPERSENSITIVITY, RESPIRATORY HYPERSENSITIVITY, ASTHMA

BRUCELLACEAE

SEE BACTERIA, BRUCELLACEAE*

BRUXISM

SEE DENTISTRY, BRUXISM

BUCCAL CAVITY

SEE ORAL-PHARYNGEAL, MOUTH

BULLOUS SKIN DISORDERS (GENERAL)

SEE SKIN DISORDERS, VESICULAR (GENERAL)

BURSA DEPENDENT IMMUNE SYSTEM

SEE IMMUNITY, HUMORAL IMMUNITY

BYPASS HEART INTRACARDIAC ABNORMAL

SEE CONGENITAL ABNORMALITIES, HEART SEPTAL DEFECTS

C'

SEE IMMUNOLOGY, COMPLEMENT

C DOMAINS

SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL

C-PEPTIDE

SEE PANCREAS HORMONES, INSULIN

C-TYPE VIRUSES (GENERAL)

SEE VIRUSES, RETROVIRIDAE

C3 CONVERTASE (C2-C4)

SEE IMMUNOLOGY, COMPLEMENT

C3 FRACTIONS AS CHEMOTACTIC FACTORS

SEE IMMUNOLOGY, COMPLEMENT, CHEMOTACTIC FACTORS

C5 FRACTIONS AS CHEMOTACTIC FACTORS

SEE IMMUNOLOGY, COMPLEMENT, CHEMOTACTIC FACTORS

CA

SEE CALCIUM

CADMIUM (COMPOUNDS)

SEE METALS, HEAVY METALS, CADMIUM (COMPOUNDS)

CALCIFICATION, DENTAL PULP

SEE DENTAL PULP DISORDERS, DENTAL PULP CALCIFICATION

CALCIFICATION ENHANCING DRUGS

(CALCIUM POSITIVE BALANCE DRUGS)

P50DE-02731-15 0036 Development support for dental research institute - Optimal methods of enamel remineralization

R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues

R01DE-04616-04 Fluoride-cadmium interaction in dental caries (rats)

- ** R01DE-04819-05 Remineralization of enamel caries in vitro (human)

CALCIFICATION INHIBITORS (CALCIUM**NEGATIVE BALANCE DRUGS)**

R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues

CALCIFICATION PATHOLOGIC

SEE CALCIUM (MINERAL) IMBALANCES, CALCIFICATION PATHOLOGIC

CALCIFICATION PHYSIOLOGIC

SEE CALCIUM (MINERAL) BALANCE, CALCIFICATION PHYSIOLOGIC

CALCINOSIS

SEE CALCIUM (MINERAL) IMBALANCES, CALCIFICATION PATHOLOGIC

CALCITONIN

SEE THYROID HORMONES, (THYRO)CALCITONIN

CALCIUM

SEE ALSO NUTRITION, DIETARY CONSTITUENTS, DIETARY CALCIUM

SEE ALSO PROTEINS, CALCIUM BINDING PROTEINS

R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)

R01DE-02110-17 Salivary gland structure and function (rats)

P50DE-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions

R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)

R01DE-04385-06 Mechanism of dental caries (human)

P50DE-05139-04 0003 Clinical research center for periodontal disease

- ** R01DE-05249-02 Salivary secretion-role of calcium (mice)
- R01DE-05289-03 Fluorine ion binding by early enamel matrix proteins (rats)

- ** R23DE-05316-03 Salivary calcium binding proteins and oral disease
- N01DE-12432-00 Caries and enamel fluoride

CALCIUM, DIETARY

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY CALCIUM

CALCIUM BINDING PROTEINS

SEE PROTEINS, CALCIUM BINDING PROTEINS

CALCIUM DEPENDENT REGULATOR PROTEIN

SEE PROTEINS, CALCIUM BINDING PROTEINS

CALCIUM HYDROXIDE

R23DE-05155-02 Active principles of dental pulp therapeutic agents

CALCIUM METABOLISM DISORDERS

SEE CALCIUM (MINERAL) IMBALANCES

CALCIUM (MINERAL) BALANCE

(METABOLISM)

SEE ALSO NUTRITION, DIETARY CONSTITUENTS, DIETARY CALCIUM

SEE ALSO PROTEINS, CALCIUM BINDING PROTEINS

P01DE-01850-18 0084 Nutritional sources and metabolic roles of fluoride - Enamel, dentin and cementum in osteogenesis imperfecta (human)

P50DE-02623-14 0030 Center for oral health research - Role of mitochondria in the mineralization process (chickens)

- ** P50DE-02668-15 0088 Regional dental research center - Hypervitaminosis D in lactation
- P50DE-02668-15 0192 Regional dental research center - Skeletal actions of calcitonin in the rat
- P50DE-02668-15 0207 Regional dental research center - Effects of vitamin A and D, PTH, CT on uptake of calcium and phosphorus in enamel
- P50DE-02670-15 0035 Institute of Dental Research - Granulocyte growth and division

- ** R01DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)
- ** R01DE-03223-11 Kinetics of mineralization of teeth (human)
- R01DE-03915-08 Tooth-saliva interface phenomena and dental caries (rabbits, goats)
- ** R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)
- R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
- ** R01DE-05209-04 Metabolic pathways in bone
- R01DE-05249-02 Salivary secretion-role of calcium (mice)
- R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)
- R23DE-05316-03 Salivary calcium binding proteins and oral disease
- R01DE-05323-02 Calcium transport in developing dental tissues (frogs, rats)
- R01DE-05375-01 Surface composition of biological apatites
- R01DE-05483-02 Characterization of predentin extracellular fluid (rats)
- R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
- R01DE-05596-02 Topically-applied polymers for caries prevention
- R01DE-05632-01 Development of salivary gland secretory function (rats)
- R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)
- N01DE-12430-00 Investigation of anticaries vaccine in primates

CALCIUM (MINERAL) BALANCE,**CALCIFICATION PHYSIOLOGIC**SEE ALSO DENTAL DEVELOPMENT, DENTINOGENESIS
SEE ALSO SKELETAL SYSTEM, BONE DEVELOPMENT, OSSIFICATION NORMAL

- ** R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
- ** R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)
- ** R01DE-04141-07 Mechanism of hard tissue mineralization (human, rats)
- R01DE-04345-06 Cellular and molecular aspects of mineralization (chick embryo)
- R01DE-04486-04 Kinetics and mechanisms of action of fluorides
- ** R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
- ** R01DE-05351-02 Electron optical examination of mineralized tissues (animals)
- ** R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

CALCIUM (MINERAL) BALANCE,**DECALCIFICATION PHYSIOLOGIC**

SEE ALSO SKELETAL SYSTEM, BONE RESORPTION-REMODELING PHYSIOLOGIC

- ** R01DE-01830-19 Quantitation of enamel demineralization mechanisms

CALCIUM (MINERAL) BALANCE, PHOSPHORUS BALANCE (METABOLISM)

P01DE-01850-18 0084 Nutritional sources and metabolic roles of fluoride - Enamel, dentin and cementum in osteogenesis imperfecta (human)

P50DE-02668-15 0088 Regional dental research center - Hypervitaminosis D in lactation

P50DE-02668-15 0192 Regional dental research center - Skeletal actions of calcitonin in the rat

R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)

R01DE-05487-02 Kinetics of mineral recycling in teeth and bone

CALCIUM (MINERAL) IMBALANCES

SEE ALSO KIDNEY DISORDERS, RENAL RICKETS

SEE ALSO METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN

SEE ALSO NUTRITION, DIETARY CONSTITUENTS, DIETARY CALCIUM

SEE ALSO SKELETAL DISORDERS, ANKYLOSIS

SEE ALSO SKELETAL DISORDERS, BONE METABOLISM (GENERAL)

SEE ALSO SKELETAL DISORDERS, OSSIFICATION PATHOLOGIC

P50DE-02668-15 0192 Regional dental research center - Skeletal actions of calcitonin in the rat

R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)

CALCIUM (MINERAL) IMBALANCES,**CALCIFICATION PATHOLOGIC**

SEE ALSO SKELETAL DISORDERS, ANKYLOSIS

SEE ALSO SKELETAL DISORDERS, OSSIFICATION PATHOLOGIC

- ** R01DE-04141-07 Mechanism of hard tissue mineralization (human, rats)
- ** R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues

CALCIUM (MINERAL) IMBALANCES,**DECALCIFICATION PATHOLOGIC**

SEE ALSO SKELETAL DISORDERS, BONE RESORPTION

ABNORMAL

R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)

CALCIUM (MINERAL) IMBALANCES,**PHOSPHORUS IMBALANCE**

SEE ALSO METABOLIC DISORDERS INBORN, VITAMIN D

RESISTANT RICKETS INBORN

R01DE-05510-02 Physico-chemistry of strontium in caries lesions

CALCIUM PHOSPHATES

- ** P50DE-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins

- ** R01DE-03223-11 Kinetics of mineralization of teeth (human)
- R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)
- R01DE-04141-07 Mechanism of hard tissue mineralization (human, rats)
- ** R01DE-04192-07 SnF₂-Ca (OH) 2-H₃O₄-H₂O reaction system
- R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
- R01DE-05375-01 Surface composition of biological apatites

CALCIUM PHOSPHATES, APATITES

R01DE-01830-19 Quantitation of enamel demineralization mechanisms

- ** R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
- R01DE-02525-16 Ultrastructural histopathology of human dental enamel

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number

- CAL**
 ** RO1DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)
 ** RO1DE-04192-07 SnF₂-Ca (OH) 2-H₃O₄-H₂O reaction system
 RO1DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
 RO1DE-04705-03 Reactions of titanium fluoride with hydroxyapatite
 RO1DE-05289-03 Fluorine ion binding by early enamel matrix proteins (rats)
 RO1DE-05354-04 Prevention of dental caries (rats, human)
 ** RO1DE-05375-01 Surface composition of biological apatites
 RO1DE-05510-02 Physico-chemistry of strontium in caries lesions
 RO1DE-05596-02 Topically-applied polymers for caries prevention
 RO1DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)
- CALCIUM PHOSPHATES, HYDROXYAPATITE**
 RO1DE-01830-19 Quantitation of enamel demineralization mechanisms
 RO1DE-01912-18 Tooth enamel apatite at the atomic level (human)
 P50DE-02731-15 0036 Development support for dental research institute - Optimal methods of enamel remineralization
 RO1DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)
 RO1DE-04141-07 Mechanism of hard tissue mineralization (human, rats)
 RO1DE-04192-07 SnF₂-Ca (OH) 2-H₃O₄-H₂O reaction system
 RO1DE-04385-06 Mechanism of dental caries (human)
 RO1DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
 ** RO1DE-04600-04 Hydroxyapatite remineralization--Role of fluoride
 ** RO1DE-04614-05 Adherence of oral streptococci to hydroxyapatite
 ** RO1DE-04705-03 Reactions of titanium fluoride with hydroxyapatite
 RO1DE-05224-01 Enamel silylation as a caries prevention method (human, animals)
 RO1DE-05252-01 Bidirectional effects of subgingival dental plaque
 RO1DE-05354-04 Prevention of dental caries (rats, human)
 RO1DE-05375-01 Surface composition of biological apatites
 RO1DE-05427-01 Adherence mechanisms of oral microbes
 R23DE-05429-03 Adherence of periodontal disease-associated bacteria
 RO1DE-05436-03 Salivary proteins in bacterial aggregation/adherence
 RO1DE-05462-01 Saliva mediated aggregation of oral bacteria (human)
 RO1DE-05596-02 Topically-applied polymers for caries prevention
 RO1DE-05652-01 Biological role of lysozyme in human saliva
 RO1DE-05747-01 Monoclonal antibody analysis of s. mutans antigens
 R23DE-05749-01 Salivary proline-rich proteins--Localization/secretion (monkeys)
 R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)
 NO1DE-72409-08 Effect of strontium, lithium and fluorine on dental plaque (rats, human)
- CALCIUM PUMP**
 SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS, CALCIUM PUMP
- CALCULI DISSOLVING AGENTS**
 SEE ALSO CALCIFICATION INHIBITORS (CALCIUM NEGATIVE BALANCE DRUGS)
 RO1DE-03223-11 Kinetics of mineralization of teeth (human)
- CALCULUS, DENTAL**
 SEE DENTAL DEPOSITS
- CALMODULIN**
 SEE PROTEINS, CALCIUM BINDING PROTEINS
- CALORIC CONTENT (OF FOODS)**
 SEE NUTRITION, DIETARY CONSTITUENTS, CALORIC CONTENT
- CALORIC STIMULATION**
 SEE TEMPERATURE, HEAT, CALORIC STIMULATION
- CALVARIUM**
 SEE SKELETAL SYSTEM, SKULL
- CAMPYLOBACTER**
 SEE BACTERIA, PSEUDOMONADES, VIBRIO*
- CANCER CHEMOTHERAPY**
 SEE NEOPLASTIC THERAPY, CANCER CHEMOTHERAPY
- CANCER IMMUNODIAGNOSIS**
 SEE NEOPLASMS DIAGNOSIS, IMMUNODIAGNOSIS OF NEOPLASMS
- CANCER RADIOTHERAPY**
 SEE NEOPLASTIC THERAPY, CANCER RADIOTHERAPY
- CANCER SURGERY**
 SEE NEOPLASMS SURGERY
- CANKER SORE**
 SEE ORAL-PHARYNGEAL DISORDERS, STOMATITIS, APHTHOUS

CANNULATION

- RO1DE-06000-01 Effect of parotid function on saliva and cells

CAPILLARY BEDS

- SEE CARDIOVASCULAR SYSTEM, CAPILLARY BEDS

CAPRYLIC ACID

- SEE FATTY ACIDS, CAPRYLIC ACID

CARBOHYDRASES

- RO1DE-03578-10 Biosynthetic study of dental plaque polysaccharides
 RO1DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins
 RO1DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

CARBOHYDRASES, AMYLASE

- RO1DE-02110-17 Salivary gland structure and function (rats)
 RO1DE-04387-05 Effect of fluoride on cAMP and glucose metabolism
 RO1DE-04897-02 Functional development of salivary glands (rats)
 RO1DE-05249-02 Salivary secretion-role of calcium (mice)
 RO1DE-05251-02 Salivary gland secretory mechanisms (rats)
 R23DE-05316-03 Salivary calcium binding proteins and oral disease
 R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)
 R23DE-05985-01 Growth factors in salivary secretions

CARBOHYDRASES, ALPHA-AMYLASE

- RO1DE-04960-03 Mechanisms of salivary gland development (mice, rats)

CARBOHYDRASES, BETA-FRUCTOFURANOSIDASE

- RO1DE-03258-10 Streptococcus mutans--Dental caries mechanism (human)
 ** RO1DE-03578-10 Biosynthetic study of dental plaque polysaccharides
 ** RO1DE-03731-06 Dextran sucrose of Streptococcus sanguis

CARBOHYDRASES, ALPHA 1,4-GLUCAN GLUCOHYDROLASE

- RO1DE-03758-07 Virulence characterization and immunization against S mutans (rats, rabbits)

CARBOHYDRASES, HYALURONIDASE

- ** R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)
 ** RO1DE-05838-02 Morphogenetic role of glycosaminoglycans (chick embryo)

CARBOHYDRASES, LYSOZYME

- RO1DE-01554-20 Host factors in caries resistance (human, rats)
 RO1DE-04217-07 Effective immunity to dental caries--Cellular basis
 ** RO1DE-04296-07 Lysozyme--Cell surface interactions and oral defense
 RO1DE-05531-03 Salivary immune factors (human, bacteria)
 ** RO1DE-05652-01 Biological role of lysozyme in human saliva
 RO1DE-05722-02 Bactericidal activity of lactoferrin on oral flora
 R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)

CARBOHYDRATES

- SEE ALSO GLYCOLIPIDS
 SEE ALSO GLYCOPROTEINS
 SEE ALSO NUCLEOTIDES
 SEE ALSO NUTRITION, DIETARY CONSTITUENTS, DIETARY CARBOHYDRATES
 SEE ALSO OLIGOSACCHARIDES
 SEE ALSO POLYSACCHARIDES
 P50DE-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins
 RO1DE-04296-07 Lysozyme--Cell surface interactions and oral defense
 R23DE-05316-03 Salivary calcium binding proteins and oral disease
 RO1DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)
 NO1DE-12430-00 Investigation of anticaries vaccine in primates

CARBOHYDRATES, AMINO SUGARS

- SEE ALSO SUGAR ACIDS, MURAMIC ACID
 SEE ALSO SUGAR ACIDS, SIALIC ACIDS
 P50DE-02600-15 0040 Support for oral biology research center - Fate of actinomycetes viscosus components within phagocytic cells

CARBOHYDRATES, DIETARY

- SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY CARBOHYDRATES

CARBOHYDRATES, MONOSACCHARIDES

- SEE ALSO HEXOSES
 SEE ALSO PENTOSE
 RO1DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

CARBOHYDRATES, PROTEIN BOUND

- CARBOHYDRATES**
 SEE ALSO GLYCOPROTEINS

- RO1DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
 ** RO1DE-03731-06 Dextran sucrose of Streptococcus sanguis
 RO1DE-05838-02 Morphogenetic role of glycosaminoglycans (chick embryo)

CARBOHYDRATES, PYRANOSSES

- NO1DE-02427-04 Synthesizes noncarcinogenic sweeteners

CARBOHYDRATES ANALOGS

- RO1DE-03118-11 Inhibition of saccharide metabolism by oral flora

CARBOHYDRATES BIOSYNTHESIS

- ** RO1DE-03118-11 Inhibition of saccharide metabolism by oral flora
 ** RO1DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)
 ** RO1DE-03578-10 Biosynthetic study of dental plaque polysaccharides
 RO1DE-03731-06 Dextran sucrose of Streptococcus sanguis
 RO1DE-03739-09 Glycosyltransferases from oral bacteria (bacteria)
 RO1DE-04224-07 Genetics of oral microflora
 RO1DE-04957-03 Bacterial metabolites in oral diseases
 NO1DE-72409-08 Effect of strontium, lithium and fluorine on dental plaque (rats, human)

CARBOHYDRATES METABOLISM

- SEE ALSO CARBOHYDRATES BIOSYNTHESIS
 ** RO1DE-03118-11 Inhibition of saccharide metabolism by oral flora
 RO1DE-03654-09 Molecular basis of dental caries (human)
 RO1DE-04008-07 Cellular and developmental control of calcification (tissue culture)
 RO1DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutans)
 RO1DE-04795-05 Characteristics of cariogenic dental plaque
 ** RO1DE-04957-03 Bacterial metabolites in oral diseases
 RO1DE-05838-02 Morphogenetic role of glycosaminoglycans (chick embryo)

CARBOHYDRATES METABOLISM, GLUCOSE METABOLISM

- SEE ALSO HEXOSES, GLYCOLYSIS
 SEE ALSO TRICARBOXYLIC ACIDS, KREBS CYCLE
 ** RO1DE-04387-05 Effect of fluoride on cAMP and glucose metabolism
 ** RO1DE-04795-05 Characteristics of cariogenic dental plaque

CARBOHYDRATES METABOLISM DISORDERS, DIABETES

- ** P50DE-02668-15 D211 Regional dental research center - Salivary glands and their innervation in diabetes (mice)
 P50DE-02731-15 0021 Development support for dental research institute - Bacterial specificity in periodontal disease
 ** RO1DE-03318-10 The molecular nature of gingival and mucosal collagen (rat)
 R23DE-05316-03 Salivary calcium binding proteins and oral disease

CARBOHYDRATES METABOLISM DISORDERS, DIABETES, DRUG-INDUCED

- ** RO1DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)

CARBOHYDRATES METABOLISM DISORDERS, DIABETES, INSULIN-DEPENDENT DIABETES

- RO1DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)
 ** RO1DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

CARBOHYDRATES METABOLISM DISORDERS, DIABETES THERAPY

- RO1DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

CARBOHYDRATES STRUCTURE

- RO1DE-03578-10 Biosynthetic study of dental plaque polysaccharides
 RO1DE-04957-03 Bacterial metabolites in oral diseases
 RO1DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)

CARBOHYDRATES TRANSPORT (GENERAL)

- RO1DE-04897-02 Functional development of salivary glands (rats)

CARBOHYDRATES TRANSPORT, GLUCOSE TRANSPORT

- RO1DE-03258-10 Streptococcus mutans--Dental caries mechanism (human)

CARBON DIOXIDE

- SEE RESPIRATORY GASES, CARBON DIOXIDE

CARBON-NITROGEN LIGASES, IMP-L-ASPARTATE LIGASE (GDP)

- RO1DE-04657-05 Abnormal palatal development induced by hadacidin (lungi)

CARBONATES

- RO1DE-01912-18 Tooth enamel apatite at the atomic level (human)
 RO1DE-05375-01 Surface composition of biological apatites (contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

R01DE-05510-02 Physico-chemistry of strontium in caries lesions

CARBONIC ANHYDRASE

SEE DEHYDRATASES, CARBONIC ANHYDRASE

CARBOPOLYCYCLICS

SEE CYCLICS, CARBOPOLYCYCLICS

CARBOXYL GROUPS

R01DE-05327-03 Polymeric polyphosphonates on dental caries and plaque (rats)

CARBOXYLIC ACIDS, KETO ACIDS

R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

CARCINOGENESIS (GENERAL)

SEE NEOPLASTIC TRANSFORMATION, CARCINOGENESIS (GENERAL)

CARCINOGENESIS, CHEMICAL

SEE NEOPLASTIC TRANSFORMATION, CARCINOGENESIS, CHEMICAL

CARCINOGENESIS, RADIATION

SEE NEOPLASTIC TRANSFORMATION, CARCINOGENESIS, RADIATION

CARCINOGENESIS, VIRAL

SEE NEOPLASTIC TRANSFORMATION, CARCINOGENESIS, VIRAL

CARCINOGENS, CHEMICAL

SEE NEOPLASTIC TRANSFORMATION, CARCINOGENS, CHEMICAL

CARCINOMA

SEE NEOPLASMS, CARCINOMA

CARCINOMA EPIDERMOID

SEE NEOPLASMS, CARCINOMA EPIDERMOID

CARDIOVASCULAR AGENTS, VASOACTIVE AGENTS (GENERAL)

R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)

CARDIOVASCULAR AGENTS, VASODILATORS

R23DE-05967-01 Role of prostaglandin E in periodontal disease activity

CARDIOVASCULAR DISORDERS, THROMBOSIS

P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin

CARDIOVASCULAR DISORDERS, VASCULAR DISORDERS (GENERAL)

R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)

CARDIOVASCULAR FUNCTION, BLOOD CIRCULATION DYNAMICS (GENERAL)

** R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)

R23DE-05605-01 The humoral regulation of pulp circulation (rats)

CARDIOVASCULAR FUNCTION, BLOOD FLOW

SEE ALSO BLOOD STASIS

R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)

P01DE-02872-12 0060 Craniofacial dysmorphology - Sensory deficits in glomerulonephritis syndromes

R01DE-04227-07 Adaptations to changes in masticatory muscle length (monkeys)

R23DE-05155-02 Active principles of dental pulp therapeutic agents

R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)

R23DE-05605-01 The humoral regulation of pulp circulation (rats)

CARDIOVASCULAR FUNCTION, BLOOD PRESSURE

P01DE-05130-03 0006 Dental/orofacial pain-Mechanisms behavior and modulation - Acute pain in research and clinical settings

CARDIOVASCULAR PROSTHESIS

R13DE-05898-01 13th Annual International Biomaterials Symposium - 1981

CARDIOVASCULAR SURGERY, REVASCLARIZATION SURGICAL

R01DE-03794-09 Surgical-orthodontics and bone healing (monkeys)

R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)

CARDIOVASCULAR SYSTEM, ANGIOGENESIS

** P50DE-02623-14 0033 Center for oral health research - Immune system in regulation of angiogenesis

CARDIOVASCULAR SYSTEM, BLOOD SUPPLY

SEE ALSO CARDIOVASCULAR SYSTEM, CAPILLARY BEDS

R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)

CARDIOVASCULAR SYSTEM, BLOOD VESSELS (GENERAL)

** R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)

CARDIOVASCULAR SYSTEM, CAPILLARY BEDS

R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

CARDIOVASCULAR SYSTEM, ENDOTHELIUM PERMEABILITY

SEE ALSO KIDNEY FUNCTION, RENAL TUBULAR TRANSPORT
SEE ALSO PREGNANCY CIRCULATION, PLACENTAL TRANSFER
R01DE-04096-05 Biocompatibility of endodontic materials (animals)
R23DE-05967-01 Role of prostaglandin E in periodontal disease activity

CARDIOVASCULAR SYSTEM, MICROCIRCULATION

R01DE-05078-05 Craniofacial growth and remodeling (human)

CARDIOVASCULAR SYSTEM, PERIPHERAL VASCULAR SYSTEM

R01DE-05512-02 Role of macrophages in periodontal disease

CARIES

SEE DENTAL CARIES

CARRIER PROTEINS

SEE BIOLOGICAL TRANSPORT, TRANSPORT PROTEINS (SEE ALSO SPECIFICS)

CARTILAGE

SEE SKELETAL SYSTEM, CARTILAGE

CARTILAGE CELLS

SEE SKELETAL SYSTEM, CARTILAGE CELLS

CARTILAGE CIRCULATION

SEE SKELETAL SYSTEM CIRCULATION

CARTILAGE DEVELOPMENT

SEE SKELETAL SYSTEM, CARTILAGE DEVELOPMENT

CASE FINDING

SEE HEALTH CARE SERVICES, CASE FINDING AND OUTREACH

CASTING, DENTAL

SEE DENTAL MATERIALS, CASTING

CATALYSTS

SEE CHEMICAL REACTIONS, CATALYSTS

CATECHOLAMINES

SEE PHENYLALKYLAMINES, CATECHOLAMINES

CATHEPSINS

SEE PROTEASES AND PEPTIDASES, CATHEPSINS

CATION

SEE IONS, CATION

CD

SEE METALS, HEAVY METALS, CADMIUM (COMPOUNDS)

CELL ADHESION

SEE ALSO CELL-CELL INTERACTION, CELL AGGREGATION
SEE ALSO GLYCOPROTEINS, FIBRONECTIN
SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, AGGLUTINATION REACTION (AGGLUTININ)*

R01DE-03469-10 Teratogens effects on cleft palate formation (mice)

R01DE-03654-09 Molecular basis of dental caries (human)

R01DE-04174-07 Variations in the surface structures of oral bacteria

R01DE-04175-07 Variations in the surface structures of oral bacteria

** R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)

R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

** R01DE-05427-01 Adherence mechanisms of oral microbes

** R23DE-05429-03 Adherence of periodontal disease-associated bacteria

R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence

R01DE-05462-01 Saliva mediated aggregation of oral bacteria (human)

R01DE-05531-03 Salivary immune factors (human, bacteria)

** R01DE-05652-01 Biological role of lysozyme in human saliva

CELL AGGREGATION

SEE CELL-CELL INTERACTION, CELL AGGREGATION

CELL BIOLOGY (GENERAL) SEE ALSO

CELL...CYTO..*

R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)

CELL BIOLOGY STUDY SECTION

** R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)

** R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, m)

** R01DE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)

** R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)

** R01DE-05630-01 Matrix/cell surface in neural crest cell morphogenesis (mice, chick, quail)

** R01DE-05838-02 Morphogenetic role of glycosaminoglycans (chick embryo)

CELL-CELL INTERACTION

SEE ALSO CELL HYBRIDS

P50DE-02623-14 0033 Center for oral health research - Immune system in regulation of angiogenesis

** R01DE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)

R01DE-04731-05 Analysis of primary palate formation (chick embryo)

R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

R23DE-05062-03 Tissue interactions during odontogenesis

R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence

R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)

** R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)

R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)

CELL-CELL INTERACTION, CELL AGGREGATION

SEE ALSO CELL ADHESION

P50DE-02623-14 0032 Center for oral health research - Interactions of salivary agglutinins and oral bacteria

** R01DE-03715-06 Cellular assembly-Its role in facial morphogenesis (fungi)

R01DE-04296-07 Lysozyme-Cell surface interactions and oral defense

** R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

** R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence

** R01DE-05462-01 Saliva mediated aggregation of oral bacteria (human)

** R01DE-05606-02 Pili of *S. sanguis* and their role in adhesion (human, rabbits)

CELL-CELL INTERACTION, INTERCELLULAR CONNECTIONS-JUNCTIONS

SEE ALSO NERVOUS SYSTEM, NERVE ENDINGS, SYNAPSES

SEE ALSO NEUROMOTOR SYSTEM, NEUROMUSCULAR JUNCTION

R01DE-05367-02 Cranio-facial anomalies in the oel mouse

CELL CHEMOTAXIS

SEE ENVIRONMENT, ORIENTATION, CHEMOTAXIS

CELL COMMUNICATIONS

SEE CELL-CELL INTERACTION

CELL COMPONENTS

SEE ALSO BACTERIAL CAPSULE

SEE ALSO MUSCLE CELLS, SARCOMERES

SEE ALSO MUSCLES, MYOFIBRILS

SEE ALSO NERVOUS SYSTEM, NEURONS, AXONS

** P01DE-02848-11 0004 Biology of connective tissue, bones, and teeth - Embryonic basal lamina development

CELL COMPONENTS, CELL MEMBRANE

SEE ALSO BIOLOGICAL TRANSPORT, MEMBRANE PERMEABILITY AND TRANSPORT

SEE ALSO CELL COMPONENTS, ENDOPLASMIC RETICULUM

SEE ALSO LIPIDS, MEMBRANE LIPIDS

SEE ALSO MEMBRANE SURFACE (BIOLOGICAL) ACTIVITY (GENERAL)

SEE ALSO PROTEINS, MEMBRANE PROTEINS

P50DE-02668-15 0193 Regional dental research center - Metabolism of isolated ameloblasts

R01DE-03715-06 Cellular assembly-Its role in facial morphogenesis (fungi)

R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)

R01DE-04296-07 Lysozyme-Cell surface interactions and oral defense

R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues

R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

R23DE-05062-03 Tissue interactions during odontogenesis

R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)

P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations

R01DE-05251-02 Salivary gland secretory mechanisms (rats)

R01DE-05367-02 Cranio-facial anomalies in the oel mouse

R01DE-05414-02 The local immune response in periodontal disease (human)

R01DE-05586-01 Cell surface studies of the enamel organ (mice)

R01DE-05630-01 Matrix/cell surface in neural crest cell morphogenesis (mice, chick, quail)

R01DE-05640-01 Cytotoxicity of periodontopathic bacteria

R01DE-05696-01 Streptococcus mutans interaction with animal tissue (also human)

R23DE-05887-01 Effects of oral bacteria on epithelium in vitro

R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

CELL COMPONENTS, CELL STROMA

R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects. See Appendix for investigator's name and Grant Number.

CELL COMPONENTS, CELL WALL

- P50DE-02600-15 0040 Support for oral biology research center - Fate of actinomycetes viscosus components within phagocytic cells
- R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)
- R01DE-03487-10 Inhibition of human cariogenic streptococci
- R01DE-05017-03 Characterization of surface antigens of *S. mutans*
- R01DE-05427-01 Adherence mechanisms of oral microbes
- R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)
- R01DE-05696-01 Streptococcus mutans interaction with animal tissue (also human)
- R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

CELL COMPONENTS, CILIARY AND FLAGELLAR MOVEMENT

- R01DE-04645-04 A genetic-biochemical analysis of spirochete motility

CELL COMPONENTS, CYTOPLASM

- R01DE-05249-02 Salivary secretion-role of calcium (mice)
- R01DE-05640-01 Cytotoxicity of periodontopathic bacteria

CELL COMPONENTS, ENDOPLASMIC RETICULUM

- SEE ALSO LIPIDS, MEMBRANE LIPIDS
- SEE ALSO MEMBRANE SURFACE (BIOLOGICAL) ACTIVITY (GENERAL)
- SEE ALSO PROTEINS, MEMBRANE PROTEINS
- P50DE-02670-15 0024 Institute of Dental Research - Metabolism of connective tissue proteoglycans

CELL COMPONENTS, LYSOSOMES

- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- P50DE-02623-14 0023 Center for oral health research - Interactions of oral bacteria and polymorphonuclear leukocytes
- R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)
- R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)
- R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)
- R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)
- R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)
- R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
- ** R23DE-05424-03 Quantitative studies of lysosomes in amelogenesis (rats)
- R01DE-05512-02 Role of macrophages in periodontal disease
- R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)
- R01DE-05626-01 Role of complement in periodontal disease
- R01DE-05640-01 Cytotoxicity of periodontopathic bacteria
- R01DE-05999-01 The role of nutrition in oral health

CELL COMPONENTS, MICROFILAMENTS

- R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)
- R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)
- R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)

CELL COMPONENTS, MICROTUBULES (GENERAL)

- ** R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)
- P50DE-05139-04 0003 Clinical research center for periodontal disease
- R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)

CELL COMPONENTS, MITOCHONDRIA

- ** P50DE-02623-14 0030 Center for oral health research - Role of mitochondria in the mineralization process (chickens)
- R23DE-05424-03 Quantitative studies of lysosomes in amelogenesis (rats)

CELL COMPONENTS, ORGANELLES

- R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)
- R23DE-05424-03 Quantitative studies of lysosomes in amelogenesis (rats)
- R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)

CELL COMPONENTS, PILI

- ** R01DE-05606-02 Pili of *S. sanguis* and their role in adhesion (human, rabbits)

CELL COMPONENTS, RIBOSOMES

- R01DE-06000-01 Effect of parotid function on saliva and cells

CELL CONTROL MECHANISMS (CELL GROWTH-PROLIFERATION)

- SEE CELL GROWTH REGULATION

CELL CULTURE

- SEE TISSUE (CELL) CULTURE*

CELL CULTURE COLLECTIONS

- SEE TISSUE (CELL) CULTURE, CELL CULTURE COLLECTIONS BANKS AND REGISTRIES

CELL CYCLE, TURNOVER (POPULATION STUDIES)

- SEE POPULATION STUDIES CELL

CELL CYCLE, TURNOVER (REGULATION OF)

- SEE CELL GROWTH REGULATION

CELL DEATH

- SEE ALSO CELL DESTRUCTION, CYTOLYSIS
- SEE ALSO TOXICOLOGY, CYTOTOXICITY
- R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)
- ** R01DE-05550-01 Cell death during craniofacial embryogenesis

CELL DESTRUCTION, CYTOLYSIS

- SEE ALSO BACTERIOLYSIS
- R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

CELL DIFFERENTIATION

- SEE ALSO GROWTH AND DEVELOPMENT, HISTOGENESIS
- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
- P50DE-02600-15 0028 Support for oral biology research center - Repletion and coupling in bone volume regulation (rat)
- P50DE-02600-15 0032 Support for oral biology research center - Keratohyalin in keratinization of oral mucosa and skin (human, rats)
- P50DE-02670-15 0035 Institute of Dental Research - Granulocyte growth and division
- R01DE-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)
- R01DE-02848-11 0004 Biology of connective tissue, bones, and teeth - Embryonic basal lamina development
- R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)

- ** R01DE-03934-07 Differentiation of oral epithelium (rats)
- ** R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)
- R01DE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)
- R01DE-04511-06 Stability of differentiation--Craniofacial study (human, hamsters)
- R01DE-04731-05 Analysis of primary palate formation (chick embryo)
- R01DE-04897-02 Functional development of salivary glands (rats)
- ** R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)
- R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine
- R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
- ** R23DE-05062-03 Tissue interactions during odontogenesis
- R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
- R23DE-05142-03 Control mechanisms in salivary gland development (rats)
- ** R01DE-05190-03 Factors determining variation in adult oral mucosa
- ** R01DE-05395-02 Stem cells in oral mucosa
- R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)
- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
- R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)
- R23DE-05627-02 Effects of mechanical forces on craniofacial growth (monkeys, rabbits)
- R01DE-05630-01 Matrix/cell surface in neural crest cell morphogenesis (mice, chick, quail)
- R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)
- R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)
- R01DE-05999-01 The role of nutrition in oral health

CELL DIVISION

- SEE ALSO NUCLEIC ACIDS SYNTHESIS, DNA
- ** P50DE-02670-15 0035 Institute of Dental Research - Granulocyte growth and division
- R01DE-03301-11 Connective tissue of the periodontium--Collagen maturation
- ** R01DE-05395-02 Stem cells in oral mucosa
- R01DE-05999-01 The role of nutrition in oral health

CELL DIVISION, MITOSIS

- SEE ALSO MITOGENS
- R01DE-04731-05 Analysis of primary palate formation (chick embryo)
- R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
- R01DE-05367-02 Cranio-facial anomalies in the oel mouse
- R23DE-05393-03 Factors association with hyperplasia of oral mucosa
- R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)
- R01DE-05999-01 The role of nutrition in oral health
- R01DE-06000-01 Effect of parotid function on saliva and cells

CELL DIVISION, SYNCHRONOUS CELL DIVISION

- P50DE-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus

CELL-FREE SYSTEMS

- R01DE-05144-03 Periodontal disease--Role of spirochetes (rabbits, human)

CELL GROWTH REGULATION

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
- R01DE-02110-17 Salivary gland structure and function (rats)
- R01DE-04731-05 Analysis of primary palate formation (chick embryo)
- ** R01DE-05838-02 Morphogenetic role of glycosaminoglycans (chick embryo)
- R23DE-05887-01 Effects of oral bacteria on epithelium in vitro

CELL HYBRIDS

- R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)
- R01DE-05467-02 Pathogenesis of localized bone destruction

CELL HYBRIDS, HYBRIDOMAS

- R01DE-05414-02 The local immune response in periodontal disease (human)
- R01DE-05467-02 Pathogenesis of localized bone destruction

CELL INGESTION, PHAGOCYTOSIS

- SEE ALSO CELLS, PHAGOCYTES
- R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)
- R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)
- R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)
- P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- P50DE-05139-04 0003 Clinical research center for periodontal disease
- R23DE-05331-01 Local host mechanism in periodontal disease (human, monkeys)
- R01DE-05494-02 Activation of macrophages in periodontal disease
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05512-02 Role of macrophages in periodontal disease
- R01DE-06065-01 The role of lymphoid cells in alveolar bone resorption

CELL INTERACTION

- SEE CELL-CELL INTERACTION

CELL LINES, BANKS AND REGISTRIES

- SEE TISSUE (CELL) CULTURE, CELL CULTURE COLLECTIONS BANKS AND REGISTRIES

CELL MEDIATED HYPERSENSITIVITY

- SEE HYPERSENSITIVITY, DELAYED HYPERSENSITIVITY

CELL MEMBRANE

- SEE CELL COMPONENTS, CELL MEMBRANE

CELL MIGRATION

- SEE ALSO NEOPLASTIC GROWTH, NEOPLASMS METASTASIS
- R01DE-03469-10 Teratogens effects on cleft palate formation (mice)
- ** R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)
- ** R01DE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)
- R01DE-04731-05 Analysis of primary palate formation (chick embryo)
- R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
- ** R01DE-05555-01 Cell migration in the teleost embryo
- R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)
- ** R01DE-05630-01 Matrix/cell surface in neural crest cell morphogenesis (mice, chick, quail)

CELL MOVEMENT

- SEE ALSO CELL COMPONENTS, CILIARY AND FLAGELLAR MOVEMENT

- SEE ALSO CELL MIGRATION
- R01DE-03301-11 Connective tissue of the periodontium--Collagen maturation
- R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)
- ** R01DE-04645-04 A genetic-biochemical analysis of spirochete motility
- R01DE-04731-05 Analysis of primary palate formation (chick embryo)
- R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)

CELL POPULATION STUDIES

- SEE POPULATION STUDIES CELL

CELL STROMA

- SEE CELL COMPONENTS, CELL STROMA

CELL SURFACE ACTIVITY (GENERAL)

- SEE MEMBRANE SURFACE (BIOLOGICAL) ACTIVITY (GENERAL) (contd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level
**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

CELL TYPES

- SEE ALSO CELL DIFFERENTIATION
- R01DE-05144-03 Periodontal disease--Role of spirochetes (rabbits, human)
- R01DE-05367-02 Cranio-facial anomalies in the oel mouse
- R01DE-05630-01 Matrix/cell surface in neural crest cell morphogenesis (mice, chick, quail)
- ** R01DE-92418-05 Characterize and identify pleomorphic oral bacteria

CELL VOLUME

- ** R23DE-05424-03 Quantitative studies of lysosomes in amelogenesis (rats)

CELL WALL

SEE CELL COMPONENTS, CELL WALL

CELLS, PHAGOCYTES

- SEE ALSO BLOOD AND RE SYSTEM, MACROPHAGES
- SEE ALSO BLOOD CELLS, LEUKOCYTES
- SEE ALSO CELL INGESTION, PHAGOCYTOSIS
- P50DE-02600-15 D030 Support for oral biology research center - Leukocyte function--Its role in periodontal disease (human)
- ** P50DE-02600-15 D040 Support for oral biology research center - Fate of actinomyces viscosus components within phagocytic cells
- R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)
- R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)
- R01DE-05413-02 Bone resorption in periodontal disease

CELLS, SINGLE CELL ANALYSIS

- R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)

CELLULAR IMMUNITY

SEE IMMUNITY, CELLULAR IMMUNITY (GENERAL)

CEMENTUM

SEE DENTAL STRUCTURE, CEMENTUM

CENTERS

SEE CLINICAL RESEARCH CENTERS

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

CENTRAL NERVOUS SYSTEM

SEE NERVOUS SYSTEM CENTRAL

CEPHALOMETRY

SEE BODY PHYSICAL CHARACTERISTICS, CEPHALOMETRY

CEREBELLO-MEDULLARY DYSPLASIA

SEE CONGENITAL ABNORMALITIES, BRAIN,

CEREBELLOMEDULLARY DYSPLASIA

CEREBRAL CORTEX

SEE BRAIN, CEREBRAL CORTEX

CERVIX NEOPLASMS

SEE NEOPLASMS OF REPRODUCTIVE SYSTEM FEMALE, UTERUS

NEOPLASMS, CERVIX NEOPLASMS

CHAIN LENGTH (CHEMISTRY)

SEE CHEMICAL STRUCTURE, CHAIN LENGTH

CHEDIAK-HIGASHI SYNDROME

SEE METABOLIC DISORDERS INBORN, CHEDIAK-HIGASHI SYNDROME

CHEEK

SEE ORAL-PHARYNGEAL, CHEEK

CHELATES, METAL

SEE METAL COMPLEXES

CHEMICAL ASSOCIATED CARCINOGENS

SEE NEOPLASTIC TRANSFORMATION, CARCINOGENESIS, CHEMICAL

CHEMICAL BONDS

- SEE ALSO CARBOHYDRATES, PROTEIN BOUND CARBOHYDRATES
- SEE ALSO CHEMICAL STRUCTURE, STEREOCHEMISTRY, CONFORMATIONS
- SEE ALSO DRUGS RECEPTORS
- R01DE-03731-06 Dextran sucrose of Streptococcus sanguis
- R01DE-05292-03 Biological prosthetic attachment (dog)

CHEMICAL BONDS, BINDING

- SEE ALSO PROTEIN BINDING
- R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
- R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)
- R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
- R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- ** R01DE-05027-04 Binding of fluoride by cariogenic bacteria
- R23DE-05519-02 Oxidation behavior of Ni-base crown and bridge alloys
- R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

CHEMICAL BONDS, BOND FORMATION

R01DE-04252-07 Semi and nonprecious metal-porcelain systems

CHEMICAL BONDS, CROSSLINKS

- R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
- ** P50DE-02668-15 0125 Regional dental research center - Collagen crosslinks and the fate of extracellular matrix
- P50DE-02668-15 0149 Regional dental research center - Strengths of polymers in tooth restorative materials
- ** P50DE-02668-15 0176 Regional dental research center - Collagen biochemistry and the myeloblastosis associated virus infected cells
- P50DE-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues
- P50DE-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues
- R01DE-03301-11 Connective tissue of the periodontium--Collagen maturation
- R01DE-04125-06 Gingival matrix proteins and periodontal disease (human, mammals)
- R01DE-05800-01 Formation and biochemical composition of sea mussel

CHEMICAL BONDS, DISULFIDE BONDS

- P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin

CHEMICAL BONDS, HYDROPHOBIC

- R01DE-05327-03 Polymeric polyphosphonates on dental caries and plaque (rats)
- ** R23DE-05886-01 Organic oligomers for new hydrophobic dental cements

CHEMICAL BONDS, IONIC

R01DE-03223-11 Kinetics of mineralization of teeth (human)

CHEMICAL CARCINOGENS

SEE NEOPLASTIC TRANSFORMATION, CARCINOGENS, CHEMICAL

CHEMICAL DESIGN

SEE CHEMICAL SYNTHESIS, DESIGN AND PRODUCTION (GENERAL)

CHEMICAL MODELS

SEE MODELS, CHEMICAL

CHEMICAL REACTION SITES, FUNCTIONAL GROUPS

R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)

CHEMICAL REACTIONS (DYNAMICS)

SEE ALSO CHEMICAL SYNTHESIS, DESIGN AND PRODUCTION (GENERAL)

SEE ALSO ENZYME MECHANISMS

SEE ALSO OXIDATION-REDUCTION

SEE ALSO PHOSPHORYLATION

SEE ALSO SULFATION

- R01DE-01830-19 Quantitation of enamel demineralization mechanisms
- ** R01DE-03223-11 Kinetics of mineralization of teeth (human)
- R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)
- ** R01DE-04262-07 Amalgamation kinetics on Ag-Sn (X) alloys
- R01DE-04385-06 Mechanism of dental caries (human)
- ** R01DE-04486-04 Kinetics and mechanisms of action of fluorides
- R01DE-04600-04 Hydroxyapatite remineralization--Role of fluoride
- R01DE-04705-03 Reactions of titanium fluoride with hydroxyapatite

CHEMICAL REACTIONS, CATALYSTS

- SEE ALSO ENZYMES
- P50DE-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology

CHEMICAL REACTIONS, HYDRATION-DEHYDRATION

- R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)

CHEMICAL REACTIONS, SOLVOLYSIS, HYDROLYSIS

- SEE ALSO HYDROLASES
- P50DE-02600-15 0040 Support for oral biology research center - Fate of actinomyces viscosus components within phagocytic cells
- R01DE-03739-09 Glycosyltransferases from oral bacteria (bacteria)
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- R01DE-05413-02 Bone resorption in periodontal disease
- R01DE-05494-02 Activation of macrophages in periodontal disease

CHEMICAL REACTIONS, SUBSTITUTION

- R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
- ** R01DE-05375-01 Surface composition of biological apatites

CHEMICAL STIMULATION

SEE DRUGS, PHARMACOLOGY, STIMULATION, CHEMICAL

CHEMICAL STRUCTURE

SEE ALSO CARBOHYDRATES STRUCTURE

SEE ALSO PROTEINS-PEPTIDES STRUCTURE

- R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
- P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)
- P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
- ** P50DE-02668-15 0149 Regional dental research center - Strengths of polymers in tooth restorative materials
- ** P50DE-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins
- ** P50DE-02670-15 0018 Institute of Dental Research - Structure of human secretory immunoglobulin A
- ** P50DE-02670-15 0029 Institute of Dental Research - Structure of connective tissue proteoglycans (cattle)
- R01DE-04101-07 Corrosion of precious metal alloys (human)
- R23DE-05314-03 Dental alloy corrosion research
- R01DE-05351-02 Electron optical examination of mineralized tissues (animals)
- ** R23DE-05956-01 The adhesive of Mytilus edulis

CHEMICAL STRUCTURE, CHAIN LENGTH

- R01DE-05596-02 Topically-applied polymers for caries prevention

CHEMICAL STRUCTURE, STEREOCHEMISTRY, CONFORMATIONS

- R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
- R01DE-05102-04 Potential anti-carries agents (rats)
- R01DE-05476-02 Novel peptide derived sweeteners
- R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

CHEMICAL STRUCTURE--BIOLOGICAL ACTIVITY

- SEE ALSO BIOASSAY*
- SEE ALSO ENZYME STRUCTURE
- R01DE-02525-16 Ultrastructural histopathology of human dental enamel
- P50DE-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology
- ** P50DE-02670-15 0019 Institute of Dental Research - Chemistry and molecular biology of the connective tissue protein, collagen
- ** R01DE-03118-11 Inhibition of saccharide metabolism by oral flora
- R01DE-03654-09 Molecular basis of dental caries (human)
- R01DE-03993-07 Effect of saliva on the metabolism of dental plaque
- R01DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- R23DE-05037-03 Biochemical role of zinc in teeth and bones
- R23DE-05142-03 Control mechanisms in salivary gland development (rats)
- R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)
- R01DE-05321-02 Titanium alloys in dentistry
- R01DE-05467-02 Pathogenesis of localized bone destruction
- R01DE-05476-02 Novel peptide derived sweeteners
- R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)
- R01DE-05606-02 Pili of S sanguis and their role in adhesion (human, rabbits)
- R01DE-05640-01 Cytotoxicity of periodontopathic bacteria
- R01DE-05800-01 Formation and biochemical composition of sea mussel

CHEMICAL STRUCTURE OF CARBOHYDRATES

SEE CARBOHYDRATES STRUCTURE

CHEMICAL SYNTHESIS, DESIGN AND PRODUCTION (GENERAL)

- SEE ALSO BIOLOGICAL PREPARATIONS AND STANDARDIZATION
- SEE ALSO DRUGS SYNTHESIS, DESIGN AND PRODUCTION
- P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction
- ** R01DE-05102-04 Potential anti-carries agents (rats)
- ** R23DE-05886-01 Organic oligomers for new hydrophobic dental cements

CHEMICALS (GENERAL), ELEMENTS, TRACE ELEMENTS

- SEE ALSO NUTRITION, DIETARY CONSTITUENTS, DIETARY TRACE ELEMENTS AND MINERALS
- P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel
- ** P50DE-02670-15 0036 Institute of Dental Research - Varnish and trace elements effects on enamel fluoride and dental caries (rats)
- R01DE-03223-11 Kinetics of mineralization of teeth (human)
- ** R01DE-04903-03 Trace metal uptake in cariogenic streptococcus mutans

CHEMICALS (GENERAL), MINERALS (GENERAL)

- SEE ALSO CALCIUM (MINERAL) BALANCE (METABOLISM)
- SEE ALSO CALCIUM PHOSPHATES, APATITES
- ** R01DE-01830-19 Quantitation of enamel demineralization mechanisms

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

CHEMICALS (GENERAL), ORGANIC COMPOUNDS (GENERAL)

- ** R23DE-05886-01 Organic oligomers for new hydrophobic dental cements

CHEMICALS (GENERAL), SALTS (GENERAL)

- SEE ALSO NUTRITION, DIETARY CONSTITUENTS, DIETARY SALTS
 ** P50DE-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins

CHEMILUMINESCENCE

SEE OPTICS, LIGHT EMISSION, LUMINESCENCE*

CHEMISTRY, ANALYTICAL

N01DE-12432-00 Caries and enamel fluoride

CHEMISTRY, CLINICAL, BLOOD

P01DE-05130-03 0006 Dental/orofacial pain--Mechanisms behavior and modulation - Acute pain in research and clinical settings

CHEMISTRY, ELECTROCHEMISTRY

R01DE-03601-09 Localized corrosion of dental amalgam
 R23DE-05314-03 Dental alloy corrosion research

CHEMISTRY, STOICHIOMETRY

R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
 R01DE-04385-06 Mechanism of dental caries (human)

CHEMISTRY, THERMODYNAMICS (GENERAL)

R01DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)
 R01DE-04252-07 Semi and nonprecious metal-porcelain systems
 R01DE-04385-06 Mechanism of dental caries (human)
 R01DE-05441-02 Optimization of metal-ceramic restoration design
 R23DE-05945-01 Physicochemical modifications of dental restoratives

CHEMORECEPTORS

SEE SENSE ORGANS, CHEMORECEPTORS

CHEMOTACTIC FACTORS (COMPLEMENT)

SEE IMMUNOLOGY, COMPLEMENT, CHEMOTACTIC FACTORS

CHEMOTACTIC FACTORS (LEUKOTAXIC FACTOR)

SEE HYPERSENSITIVITY, LYMPHOKINES, LEUKOTAXIC FACTOR

CHEMOTAXINS

SEE IMMUNOLOGY, COMPLEMENT, CHEMOTACTIC FACTORS

CHEMOTAXIS

SEE ENVIRONMENT, ORIENTATION, CHEMOTAXIS

CHEMOTHERAPY

SEE DRUGS, CHEMOTHERAPY

CHEMOTHERAPY, CANCER

SEE NEOPLASTIC THERAPY, CANCER CHEMOTHERAPY

CHEMOTHERAPY, CONNECTIVE TISSUE DISORDERS

SEE CONNECTIVE TISSUE DISORDERS CHEMOTHERAPY

CHEMOTHERAPY, DENTAL DISORDERS

SEE DENTAL DISORDERS CHEMOTHERAPY

CHILD BEHAVIOR

SEE CHILD MENTAL DEVELOPMENT, CHILD BEHAVIOR

CHILD DEVELOPMENT (NON-PSYCHOLOGICAL)

SEE ALSO CHILD MENTAL DEVELOPMENT
 SEE ALSO EMBRYOLOGY (HUMAN) AND DEVELOPMENT STUDY SECTION

- M P01DE-01697-19 A research program in craniofacial problems
 ** P01DE-02872-12 0035 Craniofacial dysmorphology - Natural history of cleft lip and palate--Morphoanalysis
 P01DE-02872-12 0036 Craniofacial dysmorphology - Natural history of cleft lip and palate--Malocclusion
 P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)
 P01DE-02872-12 0061 Craniofacial dysmorphology - Craniofacial dysmorphology
 R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
 P01DE-03568-07 0008 Craniofacial anomalies--Etiology and treatment - Craniofacial growth
 R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)
 R01DE-05078-05 Craniofacial growth and remodeling (human)
 R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)

CHILD DEVELOPMENT, PUBERTY

R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

CHILD HEALTH CARE (SERVICES)

- ** R23DE-05799-01 Behavioral methods for pedodontic management (human)

CHILD MENTAL DEVELOPMENT

SEE ALSO INFORMATION-COMMUNICATION BEHAVIOR, LANGUAGE DEVELOPMENT

P01DE-01697-19 0039 A research program in craniofacial problems - Otitis media and its consequences (human)

CHILD MENTAL DEVELOPMENT, CHILD BEHAVIOR

- ** R01DE-04779-04 Behavioral stages for cleft palate patients
 ** R01DE-05371-01 Psychosocial evaluation of craniofacial patients
 ** R23DE-05799-01 Behavioral methods for pedodontic management (human)

CHILD-MOTHER INTERACTION

SEE FAMILY, PARENT-OFFSPRING, MOTHER-CHILD INTERACTION

CHILDREN

SEE ALSO FAMILY

- R01DE-01554-20 Host factors in caries resistance (human, rats)
 M P01DE-01697-19 A research program in craniofacial problems
 ** P01DE-01697-19 0037 A research program in craniofacial problems - Effects of oronasal fistulae on speech (human)
 ** P01DE-01697-19 0041 A research program in craniofacial problems - Effect of palate repair on eustachian tube function (human)
 P01DE-02847-13 0021 Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)
 P01DE-02847-13 0022 Microbial ecology and its relation to dental disease - Cemental caries as a dental problem (human, rats, primates)
 P01DE-02872-12 0034 Craniofacial dysmorphology - Digitization of roentgencephalometric data (human)
 P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)
 P01DE-03568-07 0008 Craniofacial anomalies--Etiology and treatment - Craniofacial growth
 ** P01DE-03568-07 0013 Craniofacial anomalies--Etiology and treatment - Pedodontics
 R01DE-04278-06 Human saliva-streptococcal metabolic interactions
 R01DE-04779-04 Behavioral stages for cleft palate patients
 ** R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years
 R01DE-05129-04 Improvement of preventive and restorative materials
 ** R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)
 R01DE-05410-02 Orthodontic treatment effects on craniofacial growth (human)
 R01DE-05531-03 Salivary immune factors (human, bacteria)
 R01DE-05684-01 Saliva proteins--Chemistry, genetics and oral health
 P01DE-05837-01 0001 Growth, surgical, and speech aspects of cleft palate - Speech pathology (human)
 ** R01DE-05868-01 Multivariate analysis of craniofacial growth
 R23DE-05942-01 Airway factors in cleft palate dentofacial deformity
 R23DE-05951-01 Selective microbial ecology of periodontitis siblings
 R01DE-06112-01 Filled sealant as a conservative restorative material (human)
 N01DE-12431-00 Dentifrice
 ** N01DE-12432-00 Caries and enamel fluoride
 ** N01DE-92421-14 National caries prevalence survey

CHILDREN, ADOLESCENCE (12 TO 21 YRS)

R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
 R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years

CHILDREN, HANDICAPPED CHILDREN

P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)
 P01DE-05837-01 0004 Growth, surgical, and speech aspects of cleft palate - Surgery (human, animals)

CHILDREN, INFANT (BIRTH TO 1 YR)

P01DE-01697-19 0039 A research program in craniofacial problems - Otitis media and its consequences (human)
 P01DE-01850-18 0071 Nutritional sources and metabolic roles of fluoride - Fluoride content of infant, toddler and adult foods
 P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)
 P01DE-02872-12 0061 Craniofacial dysmorphology - Craniofacial dysmorphology
 P01DE-05837-01 0004 Growth, surgical, and speech aspects of cleft palate - Surgery (human, animals)

CHILDREN, INFANT NEWBORN (BIRTH TO 4-6 WKS)

SEE ALSO CONGENITAL ABNORMALITIES
 P01DE-03610-15 0017 Cranio-facial growth and development - Craniofacial profile patterns in normal and malformed prenatals and postnates
 R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years
 R01DE-05078-05 Craniofacial growth and remodeling (human)

CHILDREN, INFANT PREMATURE AND LOW BIRTH WEIGHT

SEE ALSO PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)

P01DE-02872-12 0063 Craniofacial dysmorphology - Premature craniofacial synostoses (human)
 P01DE-03610-15 0017 Cranio-facial growth and development - Craniofacial profile patterns in normal and malformed prenatals and postnates

CHILDREN, MIDDLEHOOD (6 TO 12 YRS)

R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years

CHILDREN, PRESCHOOL (1 TO 6 YRS)

P01DE-01697-19 0039 A research program in craniofacial problems - Otitis media and its consequences (human)
 R01DE-04157-08 Functional mandibular movements (human)
 R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years
 R01DE-05078-05 Craniofacial growth and remodeling (human)

CHIMERAS

SEE TISSUE MOSAICISM

CHL-A LOCUS (CHIMPANZEE)

SEE IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)

CHLORHEXIDINE

SEE GUANIDINES, BIGUANIDES, CHLORHEXIDINE

CHLORIDE PUMP

SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS, CHLORIDE PUMP

CHLORIDES

SEE HALOGENS, CHLORINE (COMPOUNDS) SEE ALSO SPECIFICS

CHLORINE (COMPOUNDS)

SEE HALOGENS, CHLORINE (COMPOUNDS) SEE ALSO SPECIFICS

7-CHLORO-7-DEOXYLINCOMYCIN HYDROCHLORIDE

SEE ANTIBIOTICS, LINCOMYCIN, CLINDAMYCIN

CHOLINE, ACETYLCHOLINE

SEE ALSO NEUROPHARMACOLOGICAL AGENTS, PARASYMPATHOMIMETIC

SEE ALSO NEUROTRANSMITTERS RECEPTORS, CHOLINERGIC RECEPTORS

R01DE-03469-10 Teratogens effects on cleft palate formation (mice)

R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

R23DE-05605-01 The humoral regulation of pulp circulation (rats)

CHOLINERGIC AGENTS

SEE NEUROPHARMACOLOGICAL AGENTS, PARASYMPATHOMIMETIC

CHOLINERGIC BLOCKING AGENTS

SEE NEUROPHARMACOLOGICAL AGENTS, PARASYMPATHOLYTIC

CHOLINERGIC RECEPTORS

SEE NEUROTRANSMITTERS RECEPTORS, CHOLINERGIC RECEPTORS

CHONDROCYTES

SEE SKELETAL SYSTEM, CARTILAGE CELLS

CHONDROGENESIS

SEE SKELETAL SYSTEM, CARTILAGE DEVELOPMENT

CHONDROITINASE

(HYALURONOGLUCOSIDASE) SEE CARBOHYDRASES, HYALURONIDASE

CHONDROITIN SULFATE

SEE POLYSACCHARIDES, GLYCOSAMINOGLYCANS, CHONDROITIN SULFATE

CHONDROMUCOPROTEINS

SEE PROTEOGLYCANS

CHORION

SEE PREGNANCY MEMBRANES, CHORION

CHROMATIN

SEE GENETICS, CHROMOSOMES, CHROMATIN

CHROMIUM (COMPOUNDS)

SEE METALS, HEAVY METALS, CHROMIUM (COMPOUNDS)

CHRONIC DISEASES (DISORDERS)

SEE DISEASES, CHRONIC (GENERAL)

CHRONIC TREATMENT, DRUGS

SEE DOSAGE AND ROUTE, RATE AND DURATION OF ADMINISTRATION

CI GENES

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

CIGARETTE SMOKING

SEE PSYCHOLOGY, HABITS, SMOKING

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**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects. See Appendix for investigator's name and Grant Number.

(contd.)

CIGAR SMOKING

SEE PSYCHOLOGY, HABITS, SMOKING

CILIARY MOVEMENT

SEE CELL COMPONENTS, CILIARY AND FLAGELLAR MOVEMENT

CIRCADIAN RHYTHMS

SEE BIOPERIODICITY, CIRCADIAN RHYTHMS

CIRCULATIONSEE CARDIOVASCULAR FUNCTION, BLOOD CIRCULATION
DYNAMICS (GENERAL)
SEE SKELETAL SYSTEM CIRCULATION**CITIES**

SEE SOCIOENVIRONMENT, URBAN AREAS

CITRIC ACID CYCLE

SEE TRICARBOXYLIC ACIDS, KREBS CYCLE

CL

SEE HALOGENS, CHLORINE (COMPOUNDS) SEE ALSO SPECIFICS

CLEARINGHOUSES

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

CLEFT LIPSEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL,
CLEFT LIP**CLEFT PALATE**SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL,
CLEFT PALATE**CLEFT PALATE PROSTHESIS**

SEE ORAL-FACIAL RESTORATION, CLEFT PALATE PROSTHESIS

CLEOCIN

SEE ANTIBIOTICS, LINCOMYCIN, CLINDAMYCIN

CLINDAMYCIN

SEE ANTIBIOTICS, LINCOMYCIN, CLINDAMYCIN

CLINICAL DATA COMPUTER PROCESSINGSEE BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER
PROCESSING OF CLINICAL DATA**CLINICAL RESEARCH CENTERS**M P50DE-04881-05 Center for clinical research in periodontal
diseases

M P50DE-04898-05 Periodontal disease research center

M P50DE-05139-04 Clinical research center for periodontal
disease**CLONE CELLS**

SEE TISSUE (CELL) CULTURE, CLONE CELLS*

**CLONING OF NUCLEIC ACIDS, GENES AND
PLASMIDS**

SEE NUCLEIC ACIDS CLONING

CO

SEE METALS, HEAVY METALS, COBALT (COMPOUNDS)

COBALT (COMPOUNDS)

SEE METALS, HEAVY METALS, COBALT (COMPOUNDS)

COCARCINOGENSSEE NEOPLASTIC TRANSFORMATION, CARCINOGENS,
COCARCINOGENS**COCCHI, GRAM-NEGATIVE**

SEE BACTERIA, GRAM-NEGATIVE*

COCCHI, GRAM-POSITIVE

SEE BACTERIA, GRAM-POSITIVE*

CODING (GENETIC)

SEE GENETICS, GENETIC CODING

CODING (NEURAL)

SEE INFORMATION PROCESSING AND CONTROL (NEURAL)

CODON

SEE GENETICS, GENETIC CODING

COENZYME IISEE PYRIDINE NUCLEOTIDES, NICOTINAMIDE RIBOTIDES,
NADP(H₂)**COGNITION**

SEE PSYCHOLGY, COGNITION

**COGNITIVE CONTROL OF VISCERAL
RESPONSES**SEE PSYCHOLGY, CONDITIONING, AUTOGENIC AND INTERNAL
CONTROL**COLCHICINE**

SEE ALKALOIDS, COLCHICINE

COLD

SEE TEMPERATURE, COLD

COLD INSOLUBLE GLOBULIN (CIG)

SEE GLYCOPROTEINS, FIBRONECTIN

COLLABORATIVE STUDY

SEE COOPERATIVE STUDY

COLLAGEN

SEE ALBUMINOIDS, COLLAGEN

COLLAGEN DISEASES

SEE CONNECTIVE TISSUE DISORDERS, COLLAGEN DISEASES

COLLAGENASE

SEE PROTEASES AND PEPTIDASES, COLLAGENASE

COMBINATION ANTINEOPLASTIC THERAPYSEE NEOPLASTIC THERAPY, COMBINATION ANTINEOPLASTIC
THERAPY**COMBINATION CHEMOTHERAPY**

SEE DRUGS, CHEMOTHERAPY, DRUGS COMBINATION

COMMUNICABLE DISEASE CONTROLSEE ALSO IMMUNITY, IMMUNIZATION (IMMUNOTHERAPY)
SEE ALSO INJURY (HAZARDS) PREVENTION AND CONTROL,
BIOHAZARDS (CONTROL)

R01DE-04504-03 Plaque bacteria as predictors of human

dental caries

R23DE-05006-03 Maternal malnutrition--Pregnancy

immunology (human)

**COMMUNICABLE DISEASE CONTROL, GERM-
FREE**R01DE-03758-07 Virulence characterization and immunization
against S mutants (rats, rabbits)**COMMUNICABLE DISEASE CONTROL AGENTS**

SEE ALSO ANTIBIOTICS

P50DE-02731-15 0021 Development support for dental

research institute - Bacterial specificity in periodontal disease

** R01DE-04744-04 New antimicrobial agents for preventing oral
diseasesN01DE-12433-00 Phase contrast evaluation of subgingival
plaque (human)**COMMUNICABLE DISEASE CONTROL AGENTS,
ANTIBACTERIAL**

SEE ALSO ANTIBIOTICS

** R01DE-03487-10 Inhibition of human cariogenic streptococci

** R01DE-05334-02 Periodontal therapy by controlled local drug
delivery (human)

** R01DE-05531-03 Salivary immune factors (human, bacteria)

** R01DE-05722-02 Bactericidal activity of lactoferrin on oral
flora**COMMUNICABLE DISEASE CONTROL AGENTS,
ANTIVIRAL**

** P50DE-02731-15 0038 Development support for dental

research institute - Antiviral chemotherapy--Drug delivery
component** R01DE-05089-03 Oral herpes simplex--An approach to dental
therapy (hamsters)** R23DE-05572-02 NEW antiviral therapy for oral and other
herpes (mice, guinea pig, rabbits)**COMMUNICABLE DISEASES DIAGNOSIS***R01DE-03745-10 Ultrastructure of experimental periodontitis
(rats)**COMMUNICATIVE BEHAVIOR**

SEE INFORMATION-COMMUNICATION BEHAVIOR

COMMUNICATIVE SCIENCES STUDY SECTION** R01DE-03631-08 Physiological study of speech adaptation
(human)** R01DE-05203-03 Speech adaptations to orthognathic surgery
(human)**COMMUNITY DENTAL HEALTH**

SEE DENTAL HEALTH, COMMUNITY DENTAL HEALTH

COMPLEMENT

SEE IMMUNOLOGY, COMPLEMENT

COMPLEMENT RECEPTORS

SEE IMMUNOLOGY, COMPLEMENT RECEPTORS

COMPLEXES

SEE METAL COMPLEXES

COMPLIANCE OF PATIENT WITH THERAPY

SEE THERAPY COMPLIANCE

COMPLICATIONS (DISEASE ORIENTED)

SEE DISEASES, COMPLICATIONS

**COMPUTER, ARTIFICIAL INTELLIGENCE,
PATTERN RECOGNITION AND CONTROL
SYSTEMS**SEE ALSO BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER
ASSISTED DIAGNOSISSEE ALSO BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER
ASSISTED MEDICAL DECISION MAKING

SEE ALSO COMPUTER SIMULATION

SEE ALSO OPTICS, IMAGE PROCESSING ANALYSIS AND
DISPLAY*** P01DE-01697-19 0040 A research program in craniofacial
problems - Pattern recognition for reconstruction of nasal
capsular anatomy**COMPUTER, OPTICAL DATA STORAGE**** P01DE-02872-12 0034 Craniofacial dysmorphology -
Digitization of roentgencephalometric data (human)**COMPUTER ANALYSIS***R01DE-03598-07 Dentofacial effects of forces to retract the
maxilla (human)R01DE-05218-03 DNA homologies among bacteria of
periodontal diseasesR01DE-05410-02 Orthodontic treatment effects on craniofacial
growth (human)**COMPUTER ASSISTED DIAGNOSIS**SEE BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER ASSISTED
DIAGNOSIS**COMPUTER ASSISTED MEDICAL DECISION
MAKING**SEE BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER ASSISTED
MEDICAL DECISION MAKING**COMPUTER CONTROL SYSTEMS (GENERAL)**SEE COMPUTER, ARTIFICIAL INTELLIGENCE, PATTERN
RECOGNITION AND CONTROL SYSTEMS**COMPUTER DIAGNOSIS**SEE BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER ASSISTED
DIAGNOSIS**COMPUTER GRAPHICS**

SEE COMPUTER PRINTING-GRAPHICS (GENERAL)

COMPUTER INFORMATION RETRIEVAL

SEE INFORMATION SYSTEMS, INFORMATION RETRIEVAL

**COMPUTER PATTERN RECOGNITION (OTHER
THAN IMAGE-WAVESHAPE, OR COMPUTER
SIMULATION OR DIAGNOSIS)**SEE COMPUTER, ARTIFICIAL INTELLIGENCE, PATTERN
RECOGNITION AND CONTROL SYSTEMS**COMPUTER PRINTING-GRAPHICS (GENERAL)**SEE ALSO OPTICS, IMAGE PROCESSING ANALYSIS AND
DISPLAY*P01DE-02872-12 0018 Craniofacial dysmorphology - Date
bank-Computerization of clinical dataR01DE-04610-03 Physiological studies on mastication
(human)

** R01DE-04990-03 Normal and abnormal faces (human)

** R01DE-05582-01 Computer graphic analysis of cranio-facial
morphology**COMPUTER PROCESSING OF BIOMEDICAL
DATA (GENERAL)**SEE BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER
PROCESSING OF LABORATORY DATA (GENERAL)**COMPUTER PROCESSING OF CLINICAL DATA**SEE BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER
PROCESSING OF CLINICAL DATA**COMPUTER PROCESSING OF LABORATORY
(BIOMEDICAL) DATA (GENERAL)**SEE BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER
PROCESSING OF LABORATORY DATA (GENERAL)**COMPUTER PROGRAMMING***

P01DE-02872-12 0034 Craniofacial dysmorphology -

Digitization of roentgencephalometric data (human)

P01DE-02872-12 0056 Craniofacial dysmorphology - Center

for craniofacial anomalies

R01DE-04068-07 Statistical methods in dental research

R01DE-05136-03 Osteoclast origin and histogenesis in
periodontium (rats)**COMPUTER SIMULATION**

SEE ALSO MODELS, MATHEMATICAL

P01DE-02872-12 0034 Craniofacial dysmorphology -

Digitization of roentgencephalometric data (human)

R01DE-03953-07 Force systems from orthodontic appliances

R01DE-04296-07 Lysozyme--Cell surface interactions and oral
defenseR01DE-04600-04 Hydroxyapatite remineralization--Role of
fluorideR01DE-04610-03 Physiological studies on mastication
(human)

** R01DE-04990-03 Normal and abnormal faces (human)

R01DE-05136-03 Osteoclast origin and histogenesis in

periodontium (rats)

R01DE-05180-03 Composition of S mutants in different growth

environments

R01DE-05292-03 Biological prosthetic attachment (dog)

R01DE-05423-02 Diffuse reflectance by esthetic dental

materials

R01DE-05582-01 Computer graphic analysis of cranio-facial
morphology**COMPUTERIZED DATA BANKS**

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

COMPUTERIZED HEALTH RECORDS

SEE HEALTH RECORDS (SYSTEMS) AUTOMATED

COMPUTERIZED INFORMATION SYSTEMS

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

COMPUTERIZED MEDICAL RECORDS

SEE HEALTH RECORDS (SYSTEMS) AUTOMATED

CONALBUMIN

SEE ALBUMINS, CONALBUMIN

CONCANAVALIN A

SEE PLANTS PROTEINS, LECTINS, CONCANAVALIN A

CONDITIONING (AUTOGENIC)(BIOFEEDBACK)SEE PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL
CONTROL**CONDITIONING THERAPY (BEHAVIOR)**

SEE PSYCHOTHERAPY, BEHAVIOR MODIFICATION

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
**Oriented significantly to above subject.M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

CONDYLE MANDIBULAR

SEE ORAL-PHARYNGEAL, JAW, MANDIBULAR CONDYLE

CONFERENCES

SEE INFORMATION DISSEMINATION, MEETINGS CONFERENCES SYMPOSIA

CONFORMATIONS (CHEMISTRY)

SEE CHEMICAL STRUCTURE, STEREOCHEMISTRY, CONFORMATIONS

CONGENITAL ABNORMALITIES

SEE ALSO GENETIC DISORDERS (SEE ALSO APPROPRIATE CONGENITAL ABNORMALITIES)

SEE ALSO METABOLIC DISORDERS INBORN

P50DE-05139-04 0003 Clinical research center for periodontal disease

- ** R01DE-05771-01 Quantitative dental traits in man--Major gene effects

CONGENITAL ABNORMALITIES, BRAIN, ANENCEPHALUS

R01DE-05078-05 Craniofacial growth and remodeling (human)

CONGENITAL ABNORMALITIES, BRAIN, CEREBELLOMEDULLARY DYSPLASIA

P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

CONGENITAL ABNORMALITIES, DENTITION

R01DE-03631-08 Physiological study of speech adaptation (human)

R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate

R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)

R01DE-05307-03 Orthodontic treatment with removable appliances (human, monkeys)

R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)

R01DE-05771-01 Quantitative dental traits in man--Major gene effects

R01DE-05832-01 Organization of the trigeminal mesencephalic nucleus (monkeys, opossums)

P01DE-05837-01 0002 Growth, surgical, and speech aspects of cleft palate - Maxillofacial growth (dogs, tamarins)

CONGENITAL ABNORMALITIES, DRUG INDUCED

SEE ALSO CONGENITAL ABNORMALITIES, TERATOGENIC AGENTS

- ** R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)

- ** R01DE-05041-03 Orofacial anomalies in phenytoin teratogenesis (mice, human)

R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

R01DE-05168-03 Glucocorticoid receptors and cleft palate (mice)

- ** R01DE-052452-12 Oral facial malformations in the rhesus monkey

CONGENITAL ABNORMALITIES, EAR (GENERAL)

P01DE-02872-12 0055 Craniofacial dysmorphology - Human genetics

CONGENITAL ABNORMALITIES, EAR-HEARING, DEAFNESS

- ** P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

CONGENITAL ABNORMALITIES, EYE (GENERAL)

R01DE-05367-02 Cranio-facial anomalies in the oel mouse

CONGENITAL ABNORMALITIES, FUSION**FAILURES**

SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CLEFT LIP

SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CLEFT PALATE

R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)

- ** R01DE-05322-01 Genetic analysis of birth defects involving septa (human, mice)

R01DE-05550-01 Cell death during craniofacial embryogenesis

CONGENITAL ABNORMALITIES, GASTROINTESTINAL, MEGACOLON

R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

CONGENITAL ABNORMALITIES, HEART SEPTAL DEFECTS

- ** R01DE-05322-01 Genetic analysis of birth defects involving septa (human, mice)

CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL

SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CLEFT LIP

- ** P01DE-01697-19 0040 A research program in craniofacial problems - Pattern recognition for reconstruction of nasal capsular anatomy

- ** P50DE-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)

- ** P50DE-02668-15 0212 Regional dental research center - Determination of risk related to alcohol consumption before pregnancy recognition

- M P01DE-02848-11 Biology of connective tissue, bones, and teeth

P01DE-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)

- ** P01DE-02848-11 0002 Biology of connective tissue, bones, and teeth - Steroid receptors in craniofacial teratology (mice)

P01DE-02848-11 0003 Biology of connective tissue, bones, and teeth - Mandibular morphogenesis--Embryonic neonatal and postnatal development (mice)

P01DE-02848-11 0004 Biology of connective tissue, bones, and teeth - Embryonic basal lamina development

- M P01DE-02872-12 Craniofacial dysmorphology

- ** P01DE-02872-12 0018 Craniofacial dysmorphology - Date bank--Computerization of clinical data

- ** P01DE-02872-12 0038 Craniofacial dysmorphology - Evaluation of craniofacial surgery

P01DE-02872-12 0055 Craniofacial dysmorphology - Human genetics

- ** P01DE-02872-12 0056 Craniofacial dysmorphology - Center for craniofacial anomalies

- ** P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

- ** P01DE-02872-12 0058 Craniofacial dysmorphology - Ophthalmology (human, rabbits)

- ** P01DE-02872-12 0059 Craniofacial dysmorphology - Necessary studies--Gross and microscopic

- ** P01DE-02872-12 0060 Craniofacial dysmorphology - Sensory deficits in otocraniofacial syndromes

- ** P01DE-02872-12 0061 Craniofacial dysmorphology - Craniofacial dysmorphology

- M P01DE-03568-07 Craniofacial anomalies--Etiology and treatment

- ** P01DE-03568-07 0008 Craniofacial anomalies--Etiology and treatment - Craniofacial growth

- ** P01DE-03568-07 0009 Craniofacial anomalies--Etiology and treatment - Cephalometrics

- ** P01DE-03568-07 0013 Craniofacial anomalies--Etiology and treatment -

P01DE-03610-15 0016 Cranio-facial growth and development - Craniofacial shape change and oral development

- ** P01DE-03610-15 0017 Cranio-facial growth and development - Craniofacial profile patterns in normal and malformed

prenates and postnates

R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)

- ** R01DE-04511-06 Stability of differentiation--Craniofacial study (human, hamsters)

- ** R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)

- ** R01DE-04844-04 Stress-related bone resorption--Mechanisms of action (rats)

- ** R01DE-04940-04 Muscular disorders in craniofacial malformations (human)

R01DE-04990-03 Normal and abnormal faces (human)

R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)

- ** R01DE-05024-03 Craniofacial abnormalities in mice with vitamin D resistant rickets

- R23DE-05036-03 Nocturnal masseter muscle activity and jaw dysfunction (human)

- R23DE-05037-03 Biochemical role of zinc in teeth and bones

- ** R01DE-05078-05 Craniofacial growth and remodeling (human)

- R01DE-05138-03 Visceral arches and oro-facial morphogenesis (mice, monkeys)

- ** R01DE-05145-03 Adjustive cranial skeletal growth (rats)

- ** R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)

- ** R01DE-05367-02 Cranio-facial anomalies in the oel mouse

- ** R01DE-05371-01 Psychosocial evaluation of craniofacial patients

- ** R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)

- ** R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)

R01DE-05555-01 Cell migration in the teleost embryo

R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)

- ** R01DE-05698-01 Evaluation of orthognathic surgery patients

- ** R01DE-052452-12 Oral facial malformations in the rhesus monkey

CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CLEFT LIP

P50DE-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)

P01DE-02848-11 0002 Biology of connective tissue, bones, and teeth - Steroid receptors in craniofacial teratology (mice)

- ** P01DE-02872-12 0035 Craniofacial dysmorphology - Natural history of cleft lip and palate--Morphoanalysis

- ** P01DE-02872-12 0036 Craniofacial dysmorphology - Natural history of cleft lip and palate--Malocclusion

- ** P01DE-02872-12 0037 Craniofacial dysmorphology - Natural history of cleft lip and palate--Maxillary arch

P01DE-02872-12 0038 Craniofacial dysmorphology - Evaluation of craniofacial surgery

- ** P01DE-02872-12 0053 Craniofacial dysmorphology - Maxillofacial prosthetics (human)

P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

- ** R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate

R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)

- ** R01DE-04779-04 Behavioral stages for cleft palate patients

R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years

- ** R01DE-05758-01 Genetic linkage study of cleft lip-palate in Denmark

- M P01DE-05837-01 Growth, surgical, and speech aspects of cleft palate

P01DE-05837-01 0001 Growth, surgical, and speech aspects of cleft palate - Speech pathology (human)

P01DE-05837-01 0002 Growth, surgical, and speech aspects of cleft palate - Maxillofacial growth (dogs, tamarins)

P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)

- ** P01DE-05837-01 0004 Growth, surgical, and speech aspects of cleft palate - Surgery (human, animals)

CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CLEFT PALATE

SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, PIERRE-ROBIN SYNDROME

- M P01DE-01697-19 A research program in craniofacial problems

- ** P01DE-01697-19 0035 A research program in craniofacial problems - Non-human primate model of cleft palate (monkeys)

- ** P01DE-01697-19 0036 A research program in craniofacial problems - Evaluation of velopharyngeal sphincteric function (human)

P01DE-01697-19 0037 A research program in craniofacial problems - Effects of oronasal fistulae on speech (human)

- ** P01DE-01697-19 0038 A research program in craniofacial problems - Anatomy of the posterior pharyngeal wall

P01DE-01697-19 0039 A research program in craniofacial problems - Otitis media and its consequences (human)

P01DE-01697-19 0041 A research program in craniofacial problems -

P50DE-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)

R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)

P01DE-02848-11 0002 Biology of connective tissue, bones, and teeth - Steroid receptors in craniofacial teratology (mice)

- ** P01DE-02872-12 0035 Craniofacial dysmorphology - Natural history of cleft lip and palate--Morphoanalysis

- ** P01DE-02872-12 0036 Craniofacial dysmorphology - Natural history of cleft lip and palate--Malocclusion

- ** P01DE-02872-12 0037 Craniofacial dysmorphology - Natural history of cleft lip and palate--Maxillary arch

P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

P01DE-02872-12 0062 Craniofacial dysmorphology - Congenital palatopharyngeal incompetence

P01DE-02872-12 0063 Craniofacial dysmorphology - Premature craniofacial synostoses (human)

- ** R01DE-03469-10 Teratogens effects on cleft palate formation (mice)

R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)

- ** R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)

- ** R01DE-04779-04 Behavioral stages for cleft palate patients

- ** R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years

- ** R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)

- ** R01DE-05041-03 Orofacial anomalies in phenytoin teratogenesis (mice, human)

R01DE-05078-05 Craniofacial growth and remodeling (human)

- ** R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

- ** R01DE-05168-03 Glucocorticoid receptors and cleft palate (mice)

- ** R01DE-05322-01 Genetic analysis of birth defects involving septa (human, mice)

R01DE-05367-02 Cranio-facial anomalies in the oel mouse

R01DE-05550-01 Cell death during craniofacial embryogenesis

- ** R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)

- ** R01DE-05758-01 Genetic linkage study of cleft lip-palate in Denmark

- M P01DE-05837-01 Growth, surgical, and speech aspects of cleft palate

P01DE-05837-01 0001 Growth, surgical, and speech aspects of cleft palate - Speech pathology (human)

P01DE-05837-01 0002 Growth, surgical, and speech aspects of cleft palate - Maxillofacial growth (dogs, tamarins)

P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)

- ** P01DE-05837-01 0004 Growth, surgical, and speech aspects of cleft palate - Surgery (human, animals)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

- R010E-05868-01 Multivariate analysis of craniofacial growth in clefting
- R23DE-05942-01 Airway factors in cleft palate dentofacial deformity

CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CRANIOFACIAL DYSDYSSTOSIS

- R010E-05078-05 Craniofacial growth and remodeling (human)

CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CRANIOSYNOSTOSES

- SEE ALSO CONGENITAL ABNORMALITIES, SKELETAL, ACROCEPHALOSYNDACTYLIA
- P01DE-02872-12 0063 Craniofacial dysmorphology - Premature craniofacial synostoses (human)
- R01DE-05078-05 Craniofacial growth and remodeling (human)

CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, PALATOPHARYNGEAL ABNORMALITIES

- SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CLEFT PALATE

- P01DE-02872-12 0062 Craniofacial dysmorphology - Congenital palatopharyngeal incompetence

CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, PIERRE-ROBIN SYNDROME

- R01DE-05078-05 Craniofacial growth and remodeling (human)

CONGENITAL ABNORMALITIES, SKELETAL (GENERAL)

- SEE ALSO CONGENITAL ABNORMALITIES, FUSION FAILURES
- SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL
- SEE ALSO METABOLIC DISORDERS INBORN, MARFAN SYNDROME

- SEE ALSO METABOLIC DISORDERS INBORN, MUCOPOLYSACCHARIDOSIS, LIPOCHONDRODYSSTROPHY

- SEE ALSO METABOLIC DISORDERS INBORN, OSTEOGENESIS IMPERFECTA

- SEE ALSO METABOLIC DISORDERS INBORN, OSTEOPECTOSIS
- SEE ALSO METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN

- R01DE-03794-09 Surgical-orthodontics and bone healing (monkeys)
- R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)

- R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)

CONGENITAL ABNORMALITIES, SKELETAL, ACROCEPHALOSYNDACTYLIA

- P01DE-02872-12 0038 Craniofacial dysmorphology - Evaluation of craniofacial surgery

- P01DE-02872-12 0056 Craniofacial dysmorphology - Center for craniofacial anomalies

- P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

- P01DE-02872-12 0063 Craniofacial dysmorphology - Premature craniofacial synostoses (human)
- R01DE-05078-05 Craniofacial growth and remodeling (human)

CONGENITAL ABNORMALITIES, TERATOGENIC AGENTS

- SEE ALSO CONGENITAL ABNORMALITIES, DRUG INOUCED
- P50DE-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)

- P50DE-02668-15 0212 Regional dental research center - Determination of risk related to alcohol consumption before pregnancy recognition

- P01DE-02848-11 0002 Biology of connective tissue, bones, and teeth - Steroid receptors in craniofacial teratology (mice)
- P01DE-02848-11 0003 Biology of connective tissue, bones, and teeth - Mandibular morphogenesis-Embryonic neonatal and postnatal development (mice)

- R01DE-03469-10 Teratogens effects on cleft palate formation (mice)

- R01DE-04511-06 Stability of differentiation-Craniofacial study (human, hamsters)

- R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)

- R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)

- R01DE-05041-03 Orofacial anomalies in phenytoin teratogenesis (mice, human)

- R01DE-05089-03 Oral herpes simplex-An approach to dental therapy (hamsters)

- R01DE-05168-03 Glucocorticoid receptors and cleft palate (mice)

- R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)

- R01DE-05555-01 Cell migration in the teleost embryo

- R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)

CONGENITAL DISEASES

- SEE CONGENITAL ABNORMALITIES

CONNECTIVE TISSUE (GENERAL)

- SEE ALSO ALBUMINOIDS, COLLAGEN

SEE ALSO ALBUMINOIDS, ELASTIN

SEE ALSO DENTAL STRUCTURE, PERIODONTIUM

SEE ALSO MEMBRANE, BASEMENT MEMBRANE

SEE ALSO SKELETAL SYSTEM, BONE

SEE ALSO SKELETAL SYSTEM, CARTILAGE

SEE ALSO SKELETAL SYSTEM, LIGAMENT

- P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)

- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)

- P50DE-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues

- P50DE-02670-15 0024 Institute of Dental Research - Metabolism of connective tissue proteoglycans

- P50DE-02670-15 0029 Institute of Dental Research - Structure of connective tissue proteoglycans (cattle)

- P50DE-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues

- R01DE-02774-13 Tissue interaction in palata: shelf closure (mice)

- R01DE-05078-05 Craniofacial growth and remodeling (human)

- R23DE-05393-03 Factors association with hyperplasia of oral mucosa

- R13DE-05752-01 Conference on biology of mineralized connective tissues

CONNECTIVE TISSUE, ELASTIC TISSUE

- R01DE-04990-03 Normal and abnormal faces (human)

CONNECTIVE TISSUE, MESENCHYME

- R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)

- P01DE-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)

- R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)

- R01DE-04731-05 Analysis of primary palate formation (chick embryo)

- R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine

- R01DE-05168-03 Glucocorticoid receptors and cleft palate (mice)

- R01DE-05367-02 Cranio-facial anomalies in the oel mouse

- R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)

CONNECTIVE TISSUE CELLS

SEE ALSO BLOOD AND RE SYSTEM, MACROPHAGES

SEE ALSO DENTAL STRUCTURE, ODONTOBLASTS

SEE ALSO SKELETAL SYSTEM, BONE CELLS

SEE ALSO SKELETAL SYSTEM, CARTILAGE CELLS

- R01DE-05190-03 Factors determining variation in adult oral mucosa

CONNECTIVE TISSUE CELLS, FIBROBLASTS

- P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)

- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)

- P50DE-02623-14 0026 Center for oral health research - Collagen biosynthesis in the periodontium

- P50DE-02623-14 0027 Center for oral health research - Collagenase in the periodontium

- R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)

- R01DE-04096-05 Biocompatibility of endodontic materials (animals)

- R01DE-04511-06 Stability of differentiation-Craniofacial study (human, hamsters)

- R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)

- R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)

- R01DE-05459-02 Phenytoin-Pathogenesis of gingival overgrowth (cats)

- R01DE-05495-02 Myofibroblast contraction in periodontium (rats)

- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)

- R01DE-05640-01 Cytotoxicity of periodontopathic bacteria

- R01DE-05690-01 Localization of the procollagens in dental tissues

- R01DE-05817-01 Gingival collagenase-Quantitation and localization (rabbits, mice, human)

CONNECTIVE TISSUE DEVELOPMENT

SEE ALSO SKELETAL SYSTEM, BONE DEVELOPMENT

SEE ALSO SKELETAL SYSTEM, CARTILAGE DEVELOPMENT

- R01DE-03318-10 The molecular nature of gingival and mucosal collagen (rat)

CONNECTIVE TISSUE DEVELOPMENT, FIBROGENESIS

- P01DE-02848-11 0003 Biology of connective tissue, bones, and teeth - Mandibular morphogenesis-Embryonic neonatal and postnatal development (mice)

CONNECTIVE TISSUE DISORDERS, COLLAGEN DISEASES

SEE ALSO CONNECTIVE TISSUE DISORDERS, LUPUS

ERYTHEMATOSUS SYSTEMIC

SEE ALSO CONNECTIVE TISSUE DISORDERS, SCLERODERMA

SEE ALSO METABOLIC DISORDERS INBORN, OSTEOGENESIS IMPERFECTA

- P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)

- P50DE-02670-15 0019 Institute of Dental Research - Chemistry and molecular biology of the connective tissue protein, collagen

- R01DE-03301-11 Connective tissue of the periodontium-Collagen maturation

CONNECTIVE TISSUE DISORDERS, LUPUS ERYTHEMATOSUS SYSTEMIC

- R01DE-05459-02 Phenytoin-Pathogenesis of gingival overgrowth (cats)

CONNECTIVE TISSUE DISORDERS, SCLERODERMA

- R01DE-05459-02 Phenytoin-Pathogenesis of gingival overgrowth (cats)

CONNECTIVE TISSUE DISORDERS, CHEMOTHERAPY

- P01DE-05837-01 0002 Growth, surgical, and speech aspects of cleft palate - Maxillofacial growth (dogs, tamarins)

CONSTANT REGION (CL,CH) GENES

- SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL

CONSUMER PRODUCTS, GLUES AND ADHESIVES

- SEE ALSO DENTAL MATERIALS, DENTAL ADHESIVES AND SEALANTS

- R23DE-05956-01 The adhesive of *Mytilus edulis*

CONSUMER PRODUCTS, MOUTHWASHES

- P50DE-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions

- R01DE-05596-02 Topically-applied polymers for caries prevention

- N01DE-82417-03 Effect of daily mouthrinsing with fluorides

CONTRACTILE PROTEINS

- SEE MUSCLE PROTEINS (AND CONTRACTILE PROTEINS)

CONTRACTION

- SEE MUSCLE FUNCTION, MUSCLE CONTRACTION

CONTROL

- SEE COMMUNICABLE DISEASE CONTROL

CONTROL OF BIOHAZARDS

- SEE INJURY (HAZARDS) PREVENTION AND CONTROL, BIOHAZARDS (CONTROL)

CONTROL OF VISCERAL RESPONSES BY SELF REGULATION

- SEE PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL CONTROL

CONVERTING VIRUSES

- SEE VIRUS CHARACTERISTICS, TRANSFORMING VIRUSES

COOPERATION

- SEE PSYCHOLOGY SOCIAL, COOPERATION

COOPERATIVE STUDY

- R01DE-04174-07 Variations in the surface structures of oral bacteria

- R01DE-04175-07 Variations in the surface structures of oral bacteria

COORDINATION COMPOUNDS, METAL

- SEE METAL COMPLEXES

COPING BEHAVIOR

- SEE PSYCHOLOGICAL ADAPTATION, COPING BEHAVIOR

COPOLYMERS

- SEE MOLECULAR CONDENSATIONS, COPOLYMERS

COPPER (COMPOUNDS)

- SEE METALS, HEAVY METALS, COPPER (COMPOUNDS)

CORNIFICATION

- SEE GROWTH AND DEVELOPMENT, KERATINIZATION

CORNIFICATION ABNORMAL

- SEE GROWTH ABNORMAL, KERATINIZATION ABNORMAL

CORTICOSTEROIDS

- SEE ADRENAL CORTEX HORMONES

CORTICOTROPIN

- SEE PITUITARY-DIENCEPHALON HORMONES, ACTH

CORTISONE

- SEE ADRENAL CORTEX HORMONES, CORTISONE

CORYNEBACTERIUM

- SEE BACTERIA, CORYNEFORM GROUP, CORYNEBACTERIUM*

CR

- SEE METALS, HEAVY METALS, CHROMIUM (COMPOUNDS)

CRABTREE EFFECT

- SEE HEXOSES, GLYCOLYSIS

CRANIAL ABNORMALITIES

- SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL

(conts)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

CRANIAL NERVES

SEE NERVOUS SYSTEM, CRANIAL NERVES

CRANIAL SUTURES

SEE SKELETAL SYSTEM, SKULL, CRANIAL SUTURES

CRANIOFACIAL ABNORMALITIES (GENERAL)

SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL

CRANIOFACIAL DYSOSTOSIS

SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CRANIOFACIAL DYSOSTOSIS

CRANIOSYNOSTOSES

SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CRANIOSYNOSTOSES

CRANIOTOMY

SEE SKELETAL SYSTEM, SKULL, CRANIOTOMY

CRANIUM

SEE SKELETAL SYSTEM, SKULL

CRIPPLED CHILDREN

SEE CHILDREN, HANDICAPPED CHILDREN

CROSS IMMUNITY

SEE IMMUNITY, CROSS IMMUNITY

CROSSLINKS (CHEMICAL BONDS)

SEE CHEMICAL BONDS, CROSSLINKS

CROSSOVER INDUCING TEST FOR MUTAGENS

SEE GENETICS, MUTAGENS, MUTAGEN TESTS

CROTON OIL

SEE LIPIDS, OILS, CROTON OIL

CROWNWORK

SEE DENTAL PROSTHESIS

CRYOSURGERY

SEE TEMPERATURE (BODY), HYPOTHERMIA INDUCED, CRYOSURGERY

CRYSTALLIZATION

SEE PHYSICAL PROPERTIES, CRYSTALS, CRYSTALLIZATION

CRYSTALS

SEE PHYSICAL PROPERTIES, CRYSTALS, CRYSTALLIZATION

CU

SEE METALS, HEAVY METALS, COPPER (COMPOUNDS)

CULTURE, EMBRYO, FETUS

SEE PREGNANCY, EMBRYO-FETUS CULTURE

CULTURE MEDIA

SEE GROWTH MEDIA

CULTURESSEE GROWTH MICROORGANISMS, MICROBIAL CULTURE
SEE TISSUE (CELL) CULTURE***CURETTAGE SUBGINGIVAL**

SEE DENTISTRY, SUBGINGIVAL CURETTAGE

CUTANEOUS SENSE

SEE SENSORY-PERCEPTUAL PROCESSES, SOMESTHESIS

CUTANEOUS SENSORY NERVES

SEE NERVOUS SYSTEM, AFFERENT NERVES, CUTANEOUS SENSORY NERVES

CYANIDES, ALKYL NITRILES, CYANOGENSP50DE-02668-15 0176 Regional dental research center -
Collagen biochemistry and the myeloblastosis associated virus
infected cells**CYANOGENS**

SEE CYANIDES, ALKYL NITRILES, CYANOGENS

CYBERNETICS

SEE BIOMEDICAL SYSTEMS AUTOMATED, MONITORING DEVICES

CYBERNETICS (COMPUTER ARTIFICIAL INTELLIGENCE (GENERAL))SEE COMPUTER, ARTIFICIAL INTELLIGENCE, PATTERN
RECOGNITION AND CONTROL SYSTEMS**CYBERNETICS (COMPUTER) GENERAL**SEE COMPUTER, ARTIFICIAL INTELLIGENCE, PATTERN
RECOGNITION AND CONTROL SYSTEMS**CYBERNETICS (NEURAL)**

SEE INFORMATION PROCESSING AND CONTROL (NEURAL)

CYBRIDS

SEE CELL HYBRIDS

CYCLAMATES

SEE FOOD, SWEETENING AGENTS

CYCLASE (ADENYL CYCLASE)

SEE NUCLEOTIDYL-CYCLASES, ADENYLATE CYCLASE

CYCLASE, GUANYL CYCLASE

SEE NUCLEOTIDYL-CYCLASES, GUANYLATE CYCLASE

CYCLIC AMINO ACIDS, DOPAR23DE-05956-01 The adhesive of *Mytilus edulis***CYCLIC AMINO ACIDS, HISTIDINE**R01DE-03915-08 Tooth-saliva interface phenomena and dental
caries (rabbits, goats)**CYCLIC AMINO ACIDS, PHENYLALANINE ANALOGS**

R01DE-05476-02 Novel peptide derived sweeteners

CYCLIC AMINO ACIDS, PROLINER01DE-03915-08 Tooth-saliva interface phenomena and dental
caries (rabbits, goats)R01DE-03987-07 Gingival collagen metabolism in health and
disease (human, rats)R01DE-05684-01 Saliva proteins--Chemistry, genetics and oral
health** R23DE-05749-01 Salivary proline-rich proteins--Localization/
secretion (monkeys)

R01DE-06000-01 Effect of parotid function on saliva and cells

CYCLIC AMINO ACIDS, PROLINE, HYDROXYPROLINER01DE-03987-07 Gingival collagen metabolism in health and
disease (human, rats)**CYCLIC AMINO ACIDS, TRYPTOPHAN**P50DE-02668-15 0190 Regional dental research center -
Thrombin and prothrombin**CYCLIC AMINO ACIDS, TYROSINE**P50DE-02668-15 0190 Regional dental research center -
Thrombin and prothrombinR01DE-03915-08 Tooth-saliva interface phenomena and dental
caries (rabbits, goats)**CYCLIC AMP**SEE PURINE NUCLEOTIDES, ADENINE NUCLEOTIDES, AMP
CYCLIC**CYCLIC COMPOUNDS (GENERAL)**

SEE CYCLICS (CYCLIC COMPOUNDS) GENERAL

CYCLIC GMPSEE PURINE NUCLEOTIDES, GUANINE NUCLEOTIDES, GMP
CYCLIC**CYCLIC NUCLEOSIDE MONOPHOSPHATES**

SEE NUCLEOTIDES, NUCLEOSIDE MONOPHOSPHATES CYCLIC

CYCLIC NUCLEOTIDES

SEE NUCLEOTIDES, NUCLEOSIDE MONOPHOSPHATES CYCLIC

CYCLICS (CYCLIC COMPOUNDS) GENERAL

R01DE-05476-02 Novel peptide derived sweeteners

CYCLICS, CARBOPOLYCYCLICS

SEE ALSO STEROIDS

R01DE-04814-02 New polymers for permanent soft denture
liners**CYCLICS, CARBOPOLYCYCLICS, BENZANTHRACENES**R01DE-03996-06 Low level irradiation-modification of
carcinogenesis**CYCLICS, CARBOPOLYCYCLICS, BENZOPYRENES**R01DE-05449-02 Transformation of oral mucosa by herpes
simplex virus (hamsters)**CYCLOHEXANE SULFAMIC ACID**

SEE FOOD, SWEETENING AGENTS

CYCLOPHOSPHAMIDE

SEE HALOALKYLAMINES, CYCLOPHOSPHAMIDE

CYSTEINE

SEE SULFUR AMINO ACIDS, CYSTEINE

CYSTIC FIBROSIS

SEE METABOLIC DISORDERS INBORN, CYSTIC FIBROSIS

CYTOCHEMISTRY

SEE HISTOCHEMISTRY AND CYTOCHEMISTRY (GENERAL)*

CYTOGENETICS

SEE GENETICS, CYTOGENETICS

CYTOLYSIS

SEE CELL DESTRUCTION, CYTOLYSIS

CYTOPLASM

SEE CELL COMPONENTS, CYTOPLASM

CYTOTOXICITY

SEE TOXICOLOGY, CYTOTOXICITY

CYTOXAN

SEE HALOALKYLAMINES, CYCLOPHOSPHAMIDE

DAIRY PRODUCTS

SEE FOOD, DAIRY PRODUCTS

DANLOS SYNDROMESEE METABOLIC DISORDERS INBORN, EHLERS-DANLOS
SYNDROME**DARK REPAIR (DNA)**

SEE NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)

DATA BANKS

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

DATA MANAGEMENT SYSTEMS

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

DATA MONITORING AND REPORTING SYSTEMS

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

DATA RETRIEVAL

SEE INFORMATION SYSTEMS, INFORMATION RETRIEVAL

DEAF-MUTISM

SEE CONGENITAL ABNORMALITIES, EAR-HEARING, DEAFNESS

DEAFNESS CONGENITAL

SEE CONGENITAL ABNORMALITIES, EAR-HEARING, DEAFNESS

DEATH, POST-MORTEM** P01DE-02872-12 0059 Craniofacial dysmorphology -
Necessary studies--Gross and microscopic** P01DE-02872-12 0061 Craniofacial dysmorphology -
Craniofacial dysmorphology**DECALCIFICATION PATHOLOGIC**SEE CALCIUM (MINERAL) IMBALANCES, DECALCIFICATION
PATHOLOGIC**DECALCIFICATION PHYSIOLOGIC**SEE CALCIUM (MINERAL) BALANCE, DECALCIFICATION
PHYSIOLOGIC**DECISION MAKING, COMPUTER ASSISTED MEDICAL DECISION MAKING**SEE BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER ASSISTED
MEDICAL DECISION MAKING**DECISION MAKING, HEALTH CARE EVALUATION**SEE HEALTH CARE (SERVICES) (RESOURCES) ANALYSIS AND
EVALUATION**DEGENERATIVE JOINT DISEASE**

SEE SKELETAL DISORDERS, ARTHRITIS, OSTEOARTHRITIS

DEGLUTITION

SEE GASTROINTESTINAL FUNCTION, DEGLUTITION

DEHYDRASES

SEE OXIDOREDUCTASES, DEHYDROGENASES

DEHYDRATASES, CARBONIC ANHYDRASER01DE-04345-06 Cellular and molecular aspects of
mineralization (chick embryo)R01DE-04475-04 Mineral nutrition and alveolar bone loss
(mice)**DEHYDRATED FOODS**

SEE FOOD SCIENCES AND TECHNOLOGY, DEHYDRATED FOODS

DEHYDRATION

SEE CHEMICAL REACTIONS, HYDRATION-DEHYDRATION

DEHYDROASCORBIC ACID

SEE VITAMIN C

DEHYDROGENASES

SEE OXIDOREDUCTASES, DEHYDROGENASES

DELAYED HYPERSENSITIVITY

SEE HYPERSENSITIVITY, DELAYED HYPERSENSITIVITY

DELIVERY OF HEALTH CARE

SEE HEALTH CARE SERVICES, PATIENT CARE MANAGEMENT

DEMOGRAPHY

SEE POPULATION STUDIES HUMAN

DENATURATION

SEE PROTEINS DENATURATION

DENSITY (SPECIFIC GRAVITY)

SEE PHYSICAL PROPERTIES, DENSITY (SPECIFIC GRAVITY)

DENTAL ABSCESSR01DE-04335-05 Comparison of treatment procedures used in
endodontics**DENTAL ADHESIVES**

SEE DENTAL MATERIALS, DENTAL ADHESIVES AND SEALANTS

DENTAL ALVEOLUS

SEE DENTAL STRUCTURE, DENTAL ALVEOLUS

DENTAL ANESTHESIA

SEE SENSORY DEPRESSION, ANESTHESIA DENTAL

DENTAL CALCULUS

SEE DENTAL DEPOSITS

DENTAL CARIESSEE ALSO DENTAL FILLINGS
SEE ALSO VACCINES, BACTERIAL, ANTI-CARIES VACCINER01DE-01554-20 Host factors in caries resistance (human,
rats)R01DE-01830-19 Quantitation of enamel demineralization
mechanismsP50DE-02623-14 0005 Center for oral health research -
Mechanisms of pathogenicity in two groups of periodontopathic
bacteria

P50DE-02670-15 Institute of Dental Research

** P50DE-02670-15 0014 Institute of Dental Research -
Mechanism of production of carious lesionsP50DE-02670-15 0018 Institute of Dental Research -
Structure of human secretory immunoglobulin AP50DE-02670-15 0020 Institute of Dental Research -
Nutrition-Disease proneness during dental development** P50DE-02670-15 0025 Institute of Dental Research -
Biochemical basis for the cariogenic property of *Streptococcus*
mutans (rat)

** P50DE-02670-15 0037 Institute of Dental Research -

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

- P50DE-02731-15 0019 Development support for dental research institute - Structure and maintenance of extrachromosomal DNA in streptococci
- P50DE-02731-15 0036 Development support for dental research institute - Optimal methods of enamel remineralization
- ** P50DE-02731-15 0037 Development support for dental research institute - Luminescence and polarized light in the diagnosis and treatment of caries
- P01DE-02847-13 0021 Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)
- ** P01DE-02847-13 0022 Microbial ecology and its relation to dental disease - Cemental caries as a dental problem (human, rats, primates)
- R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
- ** R01DE-03118-11 Inhibition of saccharide metabolism by oral flora
- R01DE-03180-11 Microbiologic studies of the human oral streptococci
- R01DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)
- R01DE-03223-11 Kinetics of mineralization of teeth (human)
- ** R01DE-03258-10 Streptococcus mutans-Dental caries mechanism (human)
- ** R01DE-03487-10 Inhibition of human cariogenic streptococci
- ** R01DE-03654-09 Molecular basis of dental caries (human)
- R01DE-03658-17 Genetic polymorphisms of saliva (human)
- ** R01DE-03713-06 Effect of fissure sealant on progress of dental caries (human)
- R01DE-03731-06 Dextran sucrose of Streptococcus sanguis
- R01DE-03739-09 Glycosyltransferases from oral bacteria (bacteria)
- ** R01DE-03758-07 Virulence characterization and immunization against S mutans (rats, rabbits)
- R01DE-03780-09 Permeability characteristics of dentin (dogs, human)
- R01DE-03856-07 Fluoride-selenium interaction in dental caries (rats)
- ** R01DE-03915-08 Tooth-saliva interface phenomena and dental caries (rabbits, goats)
- R01DE-03993-07 Effect of saliva on the metabolism of dental plaque
- R01DE-04068-07 Statistical methods in dental research
- R01DE-04174-07 Variations in the surface structures of oral bacteria
- R01DE-04175-07 Variations in the surface structures of oral bacteria
- R01DE-04224-07 Genetics of oral microflora
- ** R01DE-04278-06 Human saliva-streptococcal metabolic interactions
- R01DE-04296-07 Lysozyme-Cell surface interactions and oral defense
- ** R01DE-04385-06 Mechanism of dental caries (human)
- R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism
- ** R01DE-04504-03 Plaque bacteria as predictors of human dental caries
- R01DE-04529-05 Replacement therapy of dental caries (rats, monkeys)
- R01DE-04600-04 Hydroxyapatite remineralization-Role of fluoride
- R01DE-04614-05 Adherence of oral streptococci to hydroxyapatite
- ** R01DE-04615-04 Fluoride-cadmium interaction in dental caries (rats, human)
- ** R01DE-04795-05 Characteristics of cariogenic dental plaque
- ** R01DE-04819-05 Remineralization of enamel caries in vitro (human)
- R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
- ** R01DE-04903-03 Trace metal uptake in cariogenic streptococcus mutans
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- R01DE-04971-03 Human salivary antigens-Characterization (monkeys)
- R01DE-05027-04 Binding of fluoride by cariogenic bacteria
- R23DE-05037-03 Biochemical role of zinc in teeth and bones
- ** R01DE-05141-03 Cariogenic mechanisms of gingival plaque bacteria
- R23DE-05155-02 Active principles of dental pulp therapeutic agents
- R23DE-05316-03 Salivary calcium binding proteins and oral disease
- ** R01DE-05354-04 Prevention of dental caries (rats, human)
- R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence
- R01DE-05476-02 Novel peptide derived sweeteners
- ** R01DE-05510-02 Physico-chemistry of strontium in caries lesions
- R01DE-05606-02 Pili of S sanguis and their role in adhesion (human, rabbits)
- ** R23DE-05628-02 Influence of trace metals on dental health (rat)
- R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)
- R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)
- R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)
- R01DE-05684-01 Saliva proteins-Chemistry, genetics and oral health
- R23DE-05749-01 Salivary proline-rich proteins-Localization/secretion (monkeys)
- ** R01DE-05773-01 Ligand receptor interactions of cariogenic bacteria
- R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)
- R01DE-06112-01 Filled sealant as a conservative restorative material (human)
- ** R01DE-12432-00 Caries and enamel fluoride
- ** R01DE-12434-00 Identify cariogenic elements of food
- ** R01DE-62491-12 Use of mutants of cariogenic streptococci to prevent dental caries (rats)
- ** R01DE-92421-14 National caries prevalence survey
- R01DE-92422-04 Dental plaque and saliva from gastric intubated patients
- DENTAL CARIES INHIBITORS**
- SEE ALSO DENTAL DISORDERS CHEMOTHERAPY, FLUORIDE
- INGESTED
- SEE ALSO DENTAL DISORDERS CHEMOTHERAPY, FLUORIDE TREATMENTS (TOPICAL)
- SEE ALSO VACCINES, BACTERIAL, ANTI-CARIES VACCINE
- P01DE-01850-18 0085 Nutritional sources and metabolic roles of fluoride - Absorption of fluoride from dietary substances (rats)
- P01DE-01850-18 0086 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on serum alkaline phosphatase activity (mice)
- P01DE-01850-18 0087 Nutritional sources and metabolic roles of fluoride - Methodology for determining ionic fluoride content of human plasma
- P01DE-01850-18 0088 Nutritional sources and metabolic roles of fluoride - Fluoride and glycosaminoglycans in bone (mice)
- P01DE-01850-18 0089 Nutritional sources and metabolic roles of fluoride - Effect of skeletal fluoride load on retention of administered fluoride
- R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
- R01DE-02525-16 Ultrastructural histopathology of human dental enamel
- ** P50DE-02670-15 0036 Institute of Dental Research - Varnish and trace elements effects on enamel fluoride and dental caries (rats)
- ** R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)
- ** R01DE-03118-11 Inhibition of saccharide metabolism by oral flora
- R01DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)
- R01DE-03223-11 Kinetics of mineralization of teeth (human)
- ** R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)
- R01DE-03258-10 Streptococcus mutans-Dental caries mechanism (human)
- R01DE-03758-07 Virulence characterization and immunization against S mutans (rats, rabbits)
- R01DE-03993-07 Effect of saliva on the metabolism of dental plaque
- R01DE-04061-07 Salivary antibodies to S mutans-Induction and effects (monkeys)
- R01DE-04192-07 SnF2-Ca (OH) 2-H3O4-H2D reaction system
- R01DE-04217-07 Effective immunity to dental caries-Cellular basis
- R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutans)
- R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)
- ** R01DE-04486-04 Kinetics and mechanisms of action of fluorides
- ** R01DE-04529-05 Replacement therapy of dental caries (rats, monkeys)
- R01DE-04615-04 Fluoride-cadmium interaction in dental caries (rats, human)
- R01DE-04616-04 Fluoride-cadmium interaction in dental caries (rats)
- ** R01DE-04835-03 Anti-carries mechanism of fluoride complexes in vitro (human)
- R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
- R01DE-05017-03 Characterization of surface antigens of S mutans
- ** R01DE-05102-04 Potential anti-carries agents (rats)
- ** R01DE-05224-01 Enamel silylation as a caries prevention method (human, animals)
- ** R23DE-05240-03 Immunological studies-Caries and periodontal disease (mice)
- ** R01DE-05327-03 Polymeric polyphosphonates on dental caries and plaque (rats)
- R01DE-05354-04 Prevention of dental caries (rats, human)
- R01DE-05510-02 Physico-chemistry of strontium in caries lesions
- R01DE-05511-02 Evanston-Oak park fluoridation study after 25 years (human)
- R01DE-05531-03 Salivary immune factors (human, bacteria)
- ** R01DE-05596-02 Topically-applied polymers for caries prevention
- R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
- ** R01DE-02434-21 Anti-carries immunization in sub-human primates
- ** R01DE-72408-06 Cross-reacting antigens/oral flora acidogenic bacteria
- ** R01DE-72409-08 Effect of strontium, lithium and fluorine on dental plaque (rats, human)
- ** R01DE-82417-03 Effect of daily mouthrinsing with fluorides
- DENTAL CARIES VACCINE**
- SEE VACCINES, BACTERIAL, ANTI-CARIES VACCINE
- DENTAL DEPOSITS**
- ** R01DE-01554-20 Host factors in caries resistance (human, rats)
- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- R01DE-03223-11 Kinetics of mineralization of teeth (human)
- ** R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
- R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)
- DENTAL DEPOSITS, PLAQUE**
- SEE ALSO MICROBIAL MATTS
- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- P50DE-02623-14 0005 Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- ** P50DE-02623-14 0009 Center for oral health research - Oral microorganisms in periodontal health and disease (human, rats)
- ** P50DE-02623-14 0014 Center for oral health research - Surface receptors on plaque forming organisms
- P50DE-02623-14 0023 Center for oral health research - Interactions of oral bacteria and polymorphonuclear leukocytes
- P50DE-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions
- P50DE-02670-15 0025 Institute of Dental Research - Biochemical basis for the cariogenic property of Streptococcus mutans (rat)
- ** P50DE-02731-15 0021 Development support for dental research institute - Bacterial specificity in periodontal disease
- ** P01DE-02847-13 0021 Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)
- ** R01DE-03118-11 Inhibition of saccharide metabolism by oral flora
- R01DE-03180-11 Microbiologic studies of the human oral streptococci
- R01DE-03223-11 Kinetics of mineralization of teeth (human)
- R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)
- R01DE-03258-10 Streptococcus mutans-Dental caries mechanism (human)
- R01DE-03301-11 Connective tissue of the periodontium--Collagen maturation
- R01DE-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)
- R01DE-03420-09 Immune phenomena in experimental periodontal disease (rats)
- R01DE-03487-10 Inhibition of human cariogenic streptococci
- ** R01DE-03488-10 Microbial composition of developing dental plaque
- ** R01DE-03578-10 Biosynthetic study of dental plaque polysaccharides
- R01DE-03654-09 Molecular basis of dental caries (human)
- R01DE-03915-08 Tooth-saliva interface phenomena and dental caries (rabbits, goats)
- ** R01DE-03993-07 Effect of saliva on the metabolism of dental plaque
- ** R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)
- R01DE-04061-07 Salivary antibodies to S mutans-Induction and effects (monkeys)
- R01DE-04174-07 Variations in the surface structures of oral bacteria
- R01DE-04175-07 Variations in the surface structures of oral bacteria
- ** R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
- R01DE-04385-06 Mechanism of dental caries (human)
- R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
- ** R01DE-04504-03 Plaque bacteria as predictors of human dental caries
- R01DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins
- R01DE-04614-05 Adherence of oral streptococci to hydroxyapatite
- R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- R01DE-04744-04 New antimicrobial agents for preventing oral diseases
- ** R01DE-04795-05 Characteristics of cariogenic dental plaque
- P50DE-04881-05 0002 Center for clinical research in periodontal diseases - Relationship of subgingival microbiota to the etiology of periodontal diseases

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
 **Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

- ** P50DE-04881-05 0004 Center for clinical research in periodontal diseases - Relation of inflammation mediators to destructive periodontal diseases
- ** R01DE-04890-03 Plaque control-healing following periodontal surgery
- P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)
- P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
- ** R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- R23DE-05006-03 Maternal malnutrition-Pregnancy immunology (human)
- ** R23DE-05050-02 Sources of toxins from human dental plaque
- R01DE-05104-02 Periodontitis-Microbial etiology and prediction
- ** R01DE-05141-03 Cariogenic mechanisms of gingival plaque bacteria
- R01DE-05144-03 Periodontal disease-Role of spirochetes (rabbits, human)
- ** R01DE-05156-03 Immunoidentification of periodontal plaque bacteria
- R01DE-05224-01 Enamel silylation as a caries prevention method (human, animals)
- R01DE-05251-02 Salivary gland secretory mechanisms (rats)
- ** R01DE-05252-01 Bidirectional effects of subgingival dental plaque
- ** R01DE-05327-03 Polymeric polyphosphonates on dental caries and plaque (rats)
- ** R01DE-05427-01 Adherence mechanisms of oral microbes
- R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence
- R01DE-05462-01 Saliva mediated aggregation of oral bacteria (human)
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05512-02 Role of macrophages in periodontal disease
- R01DE-05531-03 Salivary immune factors (human, bacteria)
- R01DE-05606-02 Pili of *S. sanguis* and their role in adhesion (human, rabbits)
- R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)
- R01DE-05640-01 Cytotoxicity of periodontopathic bacteria
- R01DE-05684-01 Saliva proteins-Chemistry, genetics and oral health
- R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
- R01DE-05747-01 Monoclonal antibody analysis of *S. mutans* antigens
- R23DE-05749-01 Salivary proline-rich proteins-Localization/secretion (monkeys)
- R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)
- R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
- R23DE-05887-01 Effects of oral bacteria on epithelium in vitro
- R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens
- R01DE-06070-01 Antibiotic susceptibilities of periodontal bacteria
- N01DE-12430-00 Investigation of anticaries vaccine in primates
- ** N01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)
- N01DE-62491-12 Use of mutants of cariogenic streptococci to prevent dental caries (rats)
- ** N01DE-72409-08 Effect of strontium, lithium and fluorine on dental plaque (rats, human)
- N01DE-82417-03 Effect of daily mouthrinsing with fluorides
- ** N01DE-92422-04 Dental plaque and saliva from gastric intubated patients

DENTAL DEPOSITS REMOVAL

- R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- R01DE-05563-02 The blade implant-Clinical efficacy and safety (human)
- ** N01DE-72407-07 Effect of tooth-cleaning on sodium fluoride rinse
- ** N01DE-92419-02 Efficacy of prior toothcleaning on fluoride treatment

DENTAL DEVELOPMENT

- SEE ALSO CONGENITAL ABNORMALITIES, DENTITION
- SEE ALSO DENTAL STRUCTURE, AMELOBLASTS
- SEE ALSO DENTAL STRUCTURE, ENAMEL ORGAN
- SEE ALSO DENTAL STRUCTURE, ODONTOBLASTS
- ** R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
- ** P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel
- ** P50DE-02670-15 0020 Institute of Dental Research - Nutrition-Disease proneness during dental development
- ** R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)
- M P01DE-02848-11 Biology of connective tissue, bones, and teeth

- ** P01DE-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)
- ** P01DE-02848-11 0004 Biology of connective tissue, bones, and teeth - Embryonic basal lamina development
- ** R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
- P01DE-03568-07 0013 Craniofacial anomalies-Etiology and treatment -
- ** R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)
- ** R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)
- ** R01DE-04157-08 Functional mandibular movements (human)
- R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism
- R01DE-04615-04 Fluoride-cadmium interaction in dental caries (rats, human)
- R01DE-04781-02 Serial craniofacial growth in clefting-Birth to fifteen years
- R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
- ** R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine
- ** R23DE-05037-03 Biochemical role of zinc in teeth and bones
- ** R23DE-05062-03 Tissue interactions during odontogenesis
- ** R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
- ** R01DE-05145-03 Adjustive cranial skeletal growth (rats)
- ** R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
- ** R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)
- R01DE-05289-03 Fluorine ion binding by early enamel matrix proteins (rats)
- ** R01DE-05323-02 Calcium transport in developing dental tissues (frogs, rats)
- R01DE-05354-04 Prevention of dental caries (rats, human)
- R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)
- ** R01DE-05397-01 Craniofacial bone formation and muscle activity (Rhesus monkey)
- ** R01DE-05410-02 Orthodontic treatment effects on craniofacial growth (human)
- ** R01DE-05483-02 Characterization of pre-dental extracellular fluid (rats)
- R23DE-05491-02 Control of biomineralization in two species (snails)
- R23DE-05628-02 Influence of trace metals on dental health (rat)
- ** R01DE-05769-03 Ultrastructure of tooth development
- ** R01DE-05771-01 Quantitative dental traits in man-Major gene effects
- R01DE-05868-01 Multivariate analysis of craniofacial growth in clefting
- ** R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)
- R23DE-05942-01 Airway factors in cleft palate dentofacial deformity
- ** R01DE-05996-01 Alveolar bone metabolism during tooth eruption (Dogs)
- R01DE-06113-01 Determinants of fluoride in the oral environment (Dogs, rats)

DENTAL DEVELOPMENT, DENTINOGENESIS

- P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel
- R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate
- ** R01DE-05092-03 Proteins involved in dentinogenesis
- ** R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)
- R01DE-05771-01 Quantitative dental traits in man-Major gene effects

DENTAL DISCOLORATION

- ** R01DE-04136-07 Maxillofacial materials-Color study

DENTAL DISCOLORATION, DENTAL MOTTLING

- SEE ALSO HALOGEN POISONING, FLUOROSIS
- R01DE-04704-05 X-ray and sem analysis of CU rich dental amalgam
- R01DE-04814-02 New polymers for permanent soft denture liners
- R23DE-05314-03 Dental alloy corrosion research
- N01DE-82417-03 Effect of daily mouthrinsing with fluorides

DENTAL DISORDERS

- SEE ALSO CONGENITAL ABNORMALITIES, DENTITION
- SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, PALATOPHARYNGEAL ABNORMALITIES
- SEE ALSO DENTAL ABSCESS
- SEE ALSO DENTAL PULP DISORDERS
- SEE ALSO ORAL-PHARYNGEAL DISORDERS (GENERAL)
- ** P50DE-02600-15 0028 Support for oral biology research center - Repletion and coupling in bone volume regulation (rat)
- M P01DE-02847-13 Microbial ecology and its relation to dental disease
- P01DE-02847-13 0021 Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)
- R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)

- R01DE-05024-03 Craniofacial abnormalities in mice with vitamin D resistant rickets
- ** R23DE-05316-03 Salivary calcium binding proteins and oral disease
- ** R23DE-05497-02 Dental disease and work loss (human)

DENTAL DISORDERS, GINGIVAL

- ** R01DE-04501-06 Cell mediated immunity in gingival inflammation (mice)
- P50DE-04881-05 0001 Center for clinical research in periodontal diseases - Diagnosis and treatment of destructive periodontal diseases
- P50DE-04881-05 0003 Center for clinical research in periodontal diseases - Host immunologic response to oral microorganisms
- R01DE-05414-02 The local immune response in periodontal disease (human)
- R01DE-05563-02 The blade implant-Clinical efficacy and safety (human)
- R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)
- R01DE-05684-01 Saliva proteins-Chemistry, genetics and oral health
- R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens

DENTAL DISORDERS, GINGIVAL HYPERPLASIA

- ** R01DE-05459-02 Phenytoin-Pathogenesis of gingival overgrowth (cats)

DENTAL DISORDERS, GINGIVITIS

- ** P50DE-02731-15 0021 Development support for dental research institute - Bacterial specificity in periodontal disease
- P50DE-02731-15 0035 Development support for dental research institute - Immune regulation in periodontal disease
- ** R01DE-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)
- R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)
- R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)
- R01DE-04744-04 New antimicrobial agents for preventing oral diseases
- P50DE-04881-05 0001 Center for clinical research in periodontal diseases - Diagnosis and treatment of destructive periodontal diseases
- P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)
- R01DE-05054-03 Periodontal diseases-Microbiological studies
- ** P50DE-05139-04 0001 Clinical research center for periodontal disease - Microbiology
- P50DE-05139-04 0003 Clinical research center for periodontal disease
- R01DE-05144-03 Periodontal disease-Role of spirochetes (rabbits, human)
- R01DE-05413-02 Bone resorption in periodontal disease
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R23DE-05599-02 Microbiology of ligature-induced periodontitis
- R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens
- N01DE-82417-03 Effect of daily mouthrinsing with fluorides

DENTAL DISORDERS, MALOCCLUSION

- SEE ALSO DENTAL OCCLUSION
- SEE ALSO DENTISTRY, ORTHODONTICS
- ** P01DE-02872-12 0036 Craniofacial dysmorphology - Natural history of cleft lip and palate-Malocclusion
- R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
- ** R01DE-03598-07 Dentofacial effects of forces to retract the maxilla (human)
- P01DE-03610-15 0016 Cranio-facial growth and development - Craniofacial shape change and oral development
- R01DE-04157-08 Functional mandibular movements (human)
- R01DE-04414-06 Porous high density polyethylene tooth roots (monkeys)
- R01DE-04610-03 Physiological studies on mastication (human)
- R01DE-05078-05 Craniofacial growth and remodeling (human)
- R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)
- R23DE-05627-02 Effects of mechanical forces on craniofacial growth (monkeys, rabbits)
- R01DE-05771-01 Quantitative dental traits in man-Major gene effects
- R23DE-05942-01 Airway factors in cleft palate dentofacial deformity

DENTAL DISORDERS, PERIODONTAL

- SEE ALSO DENTAL DISORDERS, GINGIVAL
- SEE ALSO DENTISTRY, SUBGINGIVAL CURETTAGE
- ** R01DE-01554-20 Host factors in caries resistance (human, rats)
- ** P01DE-01850-18 0081 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on strain N mice
- ** P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

- P50DE-02600-15 0028 Support for oral biology research center - Repletion and coupling in bone volume regulation (rat)
- ** P50DE-02600-15 0030 Support for oral biology research center - Leukocyte function-Its role in periodontal disease (human)
- ** P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)
- ** P50DE-02623-14 0005 Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- ** P50DE-02623-14 0009 Center for oral health research - Oral microorganisms in periodontal health and disease (human, rats)
- P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction
- P50DE-02623-14 0023 Center for oral health research - Interactions of oral bacteria and polymorphonuclear leukocytes
- P50DE-02623-14 0026 Center for oral health research - Collagen biosynthesis in the periodontium
- P50DE-02623-14 0027 Center for oral health research - Collagenase in the periodontium
- ** P50DE-02623-14 0031 Center for oral health research - Role of immunity in periodontal disease (rats)
- P50DE-02731-15 0021 Development support for dental research institute - Bacterial specificity in periodontal disease
- ** P50DE-02731-15 0033 Development support for dental research institute - Clinical trials of periodontal therapy
- ** P50DE-02731-15 0035 Development support for dental research institute - Immune regulation in periodontal disease
- ** P01DE-02847-13 0023 Microbial ecology and its relation to dental disease - Microbiota associated with periodontal diseases (human, rats, hamsters)
- R01DE-03180-11 Microbiological studies of the human oral streptococci
- ** R01DE-03301-11 Connective tissue of the periodontium--Collagen maturation
- ** R01DE-03420-09 Immune phenomena in experimental periodontal disease (rats)
- R01DE-03488-10 Microbial composition of developing dental plaque
- R01DE-03658-17 Genetic polymorphisms of saliva (human)
- R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)
- R01DE-03915-08 Tooth-saliva interface phenomena and dental caries (rabbits, goats)
- ** R01DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)
- R01DE-03993-07 Effect of saliva on the metabolism of dental plaque
- ** R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)
- R01DE-04039-04 Sex steroid metabolism in oral tissues
- ** R01DE-04125-06 Gingival matrix proteins and periodontal disease (human, mammals)
- R01DE-04414-06 Porous high density polyethylene tooth roots (monkeys)
- R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)
- R01DE-04501-06 Cell mediated immunity in gingival inflammation (mice)
- R01DE-04529-05 Replacement therapy of dental caries (rats, monkeys)
- R01DE-04614-05 Adherence of oral streptococci to hydroxyapatite
- ** R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)
- ** R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- ** R01DE-04744-04 New antimicrobial agents for preventing oral diseases
- R01DE-04808-02 Virulence factors of gram negative corroding bacteria
- M P50DE-04881-05 Center for clinical research in periodontal diseases
- ** P50DE-04881-05 0001 Center for clinical research in periodontal diseases - Diagnosis and treatment of destructive periodontal diseases
- ** P50DE-04881-05 0002 Center for clinical research in periodontal diseases - Relationship of subgingival microbiota to the etiology of periodontal diseases
- ** P50DE-04881-05 0003 Center for clinical research in periodontal diseases - Host immunologic response to oral microorganisms
- ** P50DE-04881-05 0004 Center for clinical research in periodontal diseases - Relation of inflammation mediators to destructive periodontal diseases
- ** R01DE-04890-03 Plaque control-healing following periodontal surgery
- M P50DE-04898-05 Periodontal disease research center
- ** P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- ** P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)
- ** P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
- ** P50DE-04898-05 0004 Periodontal disease research center - Periodontal disease and the electromyographic silent period (human)
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- R01DE-04971-03 Human salivary antigens-Characterization (monkeys)
- R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
- ** R23DE-05050-02 Sources of toxins from human dental plaque
- ** R01DE-05054-03 Periodontal diseases-Microbiological studies
- ** R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)
- M P50DE-05139-04 Clinical research center for periodontal disease
- ** P50DE-05139-04 0001 Clinical research center for periodontal disease - Microbiology
- ** P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations
- ** P50DE-05139-04 0003 Clinical research center for periodontal disease
- ** R01DE-05144-03 Periodontal disease--Role of spirochetes (rabbits, human)
- ** R01DE-05155-03 Immunoidentification of periodontal plaque bacteria
- ** R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)
- ** R01DE-05218-03 DNA homologies among bacteria of periodontal diseases
- ** R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)
- R01DE-05255-03 Regulation of collagenase and bone resorption (chick embryos, mice)
- R23DE-05332-03 Bone in vitro-Ultrastructure and autoradiography (mice)
- ** R01DE-05334-02 Periodontal therapy by controlled local drug delivery (human)
- ** R01DE-05352-03 Immunochemical studies in periodontal disease
- ** R01DE-05413-02 Bone resorption in periodontal disease
- ** R01DE-05414-02 The local immune response in periodontal disease (human)
- ** R23DE-05429-03 Adherence of periodontal disease-associated bacteria
- R01DE-05462-01 Saliva mediated aggregation of oral bacteria (human)
- ** R01DE-05467-02 Pathogenesis of localized bone destruction
- ** R01DE-05494-02 Activation of macrophages in periodontal disease
- ** R01DE-05512-02 Role of macrophages in periodontal disease
- R01DE-05525-02 Nature of the permeability barrier in oral epithelium
- R01DE-05560-01 Rapid identification of oral bacteria
- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
- ** R01DE-05626-01 Role of complement in periodontal disease
- ** R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)
- ** R01DE-05640-01 Cytotoxicity of periodontopathic bacteria
- R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)
- R01DE-05684-01 Saliva proteins--Chemistry, genetics and oral health
- ** R01DE-05706-01 Role of microbial collagenases in periodontal disease
- ** R01DE-05723-01 Spirochete influence on immunity in oral disease
- ** R01DE-05729-01 Etiological mechanisms in periodontal disease
- ** R01DE-05732-02 Specificity of cell mediated immune response in periodontal disease
- R23DE-05749-01 Salivary proline-rich proteins--Localization/secretion (monkeys)
- ** R13DE-05753-01 Symposium on host-bacteria in periodontal diseases
- ** R01DE-05817-01 Gingival collagenase--Quantitation and localization (rabbits, mice, human)
- R23DE-05887-01 Effects of oral bacteria on epithelium in vitro
- R13DE-05897-01 Oral immunogenetics and tissue transplantation (symposium)
- ** R23DE-05942-01 Airway factors in cleft palate dentofacial deformity
- ** R23DE-05951-01 Selective microbial ecology of periodontitis siblings
- ** R23DE-05967-01 Role of prostaglandin E in periodontal disease activity
- ** R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens
- R01DE-06065-01 The role of lymphoid cells in alveolar bone resorption
- R01DE-06070-01 Antibiotic susceptibilities of periodontal bacteria
- DENTAL DISORDERS, PERIODONTITIS**
- ** P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- ** P50DE-02600-15 0035 Support for oral biology research center - Serotyping of microbes for diagnosis of periodontitis (rabbits)
- ** P50DE-02600-15 0037 Support for oral biology research center - Periodontal microflora (human)
- P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)
- P50DE-02731-15 0035 Development support for dental research institute - Immune regulation in periodontal disease
- ** R01DE-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)
- ** R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)
- R01DE-04744-04 New antimicrobial agents for preventing oral diseases
- P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)
- P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
- R23DE-05050-02 Sources of toxins from human dental plaque
- R01DE-05054-03 Periodontal diseases-Microbiological studies
- ** R01DE-05104-02 Periodontitis--Microbial etiology and prediction
- P50DE-05139-04 0001 Clinical research center for periodontal disease - Microbiology
- P50DE-05139-04 0003 Clinical research center for periodontal disease
- ** R01DE-05252-01 Bidirectional effects of subgingival dental plaque
- ** R23DE-05331-01 Local host mechanism in periodontal disease (human, monkeys)
- R01DE-05413-02 Bone resorption in periodontal disease
- ** R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05512-02 Role of macrophages in periodontal disease
- ** R23DE-05599-02 Microbiology of ligature-induced periodontitis
- R01DE-05640-01 Cytotoxicity of periodontopathic bacteria
- ** R01DE-05706-01 Role of microbial collagenases in periodontal disease
- ** R23DE-05793-01 Degradation of collagen in inflammation (human gingiva)
- R23DE-05942-01 Airway factors in cleft palate dentofacial deformity
- R23DE-05951-01 Selective microbial ecology of periodontitis siblings
- R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens
- ** N01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)
- DENTAL DISORDERS, TOOTH LOSS**
- SEE ALSO DENTAL EXTRACTION
- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- DENTAL DISORDERS, TOOTH RESORPTION**
- ** R01DE-03545-09 Prediction of tooth displacement (human)
- ** R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)
- R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)
- ** R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)
- R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)
- ** R01DE-04844-04 Stress-related bone resorption--Mechanisms of action (rats)
- R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05996-01 Alveolar bone metabolism during tooth eruption (Dogs)
- DENTAL DISORDERS CHEMOTHERAPY**
- SEE ALSO CONSUMER PRODUCTS, MOUTHWASHES
- P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)
- P50DE-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)
- P50DE-02731-15 0036 Development support for dental research institute - Optimal methods of enamel remineralization
- P50DE-02731-15 0038 Development support for dental research institute - Antiviral chemotherapy--Drug delivery component
- ** R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)
- R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
- ** R01DE-04744-04 New antimicrobial agents for preventing oral diseases
- P50DE-04881-05 0002 Center for clinical research in periodontal diseases - Relationship of subgingival microbiota to the etiology of periodontal diseases
- P50DE-04881-05 0004 Center for clinical research in periodontal diseases - Relation of inflammation mediators to destructive periodontal diseases
- M P50DE-04898-05 Periodontal disease research center
- P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- ** P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
- P01DE-05130-03 0006 Dental/orofacial pain--Mechanisms behavior and modulation - Acute pain in research and clinical settings
- ** R23DE-05155-02 Active principles of dental pulp therapeutic agents
- ** R01DE-05334-02 Periodontal therapy by controlled local drug delivery (human)
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
 **Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

- R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)
 R01DE-06070-01 Antibiotic susceptibilities of periodontal bacteria
 ** R01DE-06112-01 Filled sealant as a conservative restorative material (human)

DENTAL DISORDERS CHEMOTHERAPY, FLUORIDE INGESTED

- M P01DE-01850-18 Nutritional sources and metabolic roles of fluoride
 ** P01DE-01850-18 0068 Nutritional sources and metabolic roles of fluoride - Radioimmunoassay of parathyroid hormone in the rat
 P01DE-01850-18 0071 Nutritional sources and metabolic roles of fluoride - Fluoride content of infant, toddler and adult foods
 ** P01DE-01850-18 0072 Nutritional sources and metabolic roles of fluoride - Effect of fluoride on iron transport (mice)
 P01DE-01850-18 0075 Nutritional sources and metabolic roles of fluoride - Metabolic handling of perfluorooctanoic acid (rats)
 P01DE-01850-18 0081 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on strain N mice
 P01DE-01850-18 0084 Nutritional sources and metabolic roles of fluoride - Enamel, dentin and cementum in osteogenesis imperfecta (human)
 ** P01DE-01850-18 0085 Nutritional sources and metabolic roles of fluoride - Absorption of fluoride from dietary substances (rats)
 ** P01DE-01850-18 0086 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on serum alkaline phosphatase activity (mice)
 ** P01DE-01850-18 0087 Nutritional sources and metabolic roles of fluoride - Methodology for determining ionic fluoride content of human plasma
 ** P01DE-01850-18 0088 Nutritional sources and metabolic roles of fluoride - Fluoride and glycosaminoglycans in bone (mice)
 ** P01DE-01850-18 0089 Nutritional sources and metabolic roles of fluoride - Effect of skeletal fluoride load on retention of administered fluoride
 R01DE-02525-16 Ultrastructural histopathology of human dental enamel
 P50DE-02670-15 0020 Institute of Dental Research - Nutrition-Disease proneness during dental development
 R01DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)
 R01DE-03223-11 Kinetics of mineralization of teeth (human)
 ** R01DE-03856-07 Fluoride-selenium interaction in dental caries (rats)
 ** R01DE-04217-07 Effective immunity to dental caries-Cellular basis
 ** R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)
 R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism
 ** R01DE-04615-04 Fluoride-cadmium interaction in dental caries (rats, human)
 R01DE-04616-04 Fluoride-cadmium interaction in dental caries (rats)
 R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
 R01DE-05510-02 Physico-chemistry of strontium in caries lesions
 ** R01DE-05511-02 Evanston-Oak park fluoridation study after 25 years (human)
 ** R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
 R01DE-06113-01 Determinants of fluoride in the oral environment (Dogs, rats)
 ** R01DE-12432-00 Caries and enamel fluoride
 ** R01DE-82417-03 Effect of daily mouthrinsing with fluorides

DENTAL DISORDERS CHEMOTHERAPY, FLUORIDE TREATMENTS (TOPICAL)

- R01DE-01830-19 Quantitation of enamel demineralization mechanisms
 R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
 R01DE-02525-16 Ultrastructural histopathology of human dental enamel
 P50DE-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions
 ** P50DE-02670-15 0036 Institute of Dental Research - Varnish and trace elements effects on enamel fluoride and dental caries (rats)
 P50DE-02731-15 0036 Development support for dental research institute - Optimal methods of enamel remineralization
 P50DE-02731-15 0037 Development support for dental research institute - Luminescence and polarized light in the diagnosis and treatment of caries
 R01DE-04192-07 SnF₂-Ca (OH) 2-H₃O₂-H₂O reaction system
 R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)
 R01DE-04385-06 Mechanism of dental caries (human)
 ** R01DE-04486-04 Kinetics and mechanisms of action of fluorides
 ** R01DE-04600-04 Hydroxyapatite remineralization-Role of fluoride
 R01DE-04616-04 Fluoride-cadmium interaction in dental caries (rats)

- ** R01DE-04705-03 Reactions of titanium fluoride with hydroxyapatite
 R01DE-04795-05 Characteristics of cariogenic dental plaque
 ** R01DE-04835-03 Anti-caries mechanism of fluoride complexes in vitro (human)
 ** R01DE-05027-04 Binding of fluoride by cariogenic bacteria
 ** R01DE-05354-04 Prevention of dental caries (rats, human)
 R01DE-05510-02 Physico-chemistry of strontium in caries lesions
 R01DE-06113-01 Determinants of fluoride in the oral environment (Dogs, rats)
 N01DE-12431-00 Clinical trial of a combined MFP-NaF dentifrice
 ** N01DE-72407-07 Effect of tooth-cleaning on sodium fluoride rinse
 ** N01DE-82417-03 Effect of daily mouthrinsing with fluorides
 R01DE-92419-02 Efficacy of prior toothcleaning on fluoride treatment

DENTAL DISORDERS DIAGNOSIS (INCL EXAMS)*

- SEE ALSO DENTAL VISUALIZATION*
 SEE ALSO ORAL-PHARYNGEAL DISORDERS DIAGNOSIS (INCL EXAMS)*
 ** P50DE-02600-15 0035 Support for oral biology research center - Serotyping of microbes for diagnosis of periodontitis (rabbits)
 ** P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)
 ** P50DE-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)
 P50DE-02731-15 0021 Development support for dental research institute - Bacterial specificity in periodontal disease
 ** P50DE-02731-15 0037 Development support for dental research institute - Luminescence and polarized light in the diagnosis and treatment of caries
 ** P01DE-03568-07 0013 Craniofacial anomalies-Etiology and treatment -
 R01DE-03598-07 Dentofacial effects of forces to retract the maxilla (human)
 R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)
 ** R01DE-04157-08 Functional mandibular movements (human)
 R01DE-04504-03 Plaque bacteria as predictors of human dental caries
 ** P50DE-04881-05 0001 Center for clinical research in periodontal diseases - Diagnosis and treatment of destructive periodontal diseases
 M P50DE-04898-05 Periodontal disease research center
 P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
 P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
 P50DE-04898-05 0004 Periodontal disease research center - Periodontal disease and the electromyographic silent period (human)
 R23DE-05036-03 Nocturnal masseter muscle activity and jaw dysfunction (human)
 P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations
 P50DE-05139-04 0003 Clinical research center for periodontal disease
 R01DE-05352-03 Immunochemical studies in periodontal disease
 R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
 ** R01DE-05706-01 Role of microbial collagenases in periodontal disease
 ** R01DE-05723-01 Spirochete influence on immunity in oral disease
 R01DE-05771-01 Quantitative dental traits in man-Major gene effects
 R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens
 ** N01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)

DENTAL DYSPLASIA, CONGENITAL

SEE CONGENITAL ABNORMALITIES, DENTITION

DENTAL EDUCATION (HEALTH OCCUPATIONS)

SEE EDUCATION, HEALTH OCCUPATIONS, DENTAL

DENTAL EDUCATION (PREVENTIVE)

SEE EDUCATION, HEALTH EDUCATION, DENTAL

DENTAL EXAMINATIONS

SEE DENTAL DISORDERS DIAGNOSIS (INCL EXAMS)*

DENTAL EXTRACTION

- SEE ALSO DENTAL DISORDERS, TOOTH LOSS
 R01DE-04004-07 Acupuncture and perception of dental pain (human)
 R01DE-05369-03 Factors affecting dental postoperative pain

DENTAL FEAR AND ANXIETY

- R01DE-04004-07 Acupuncture and perception of dental pain (human)
 ** R01DE-04494-05 Control of stress during dental procedures (human)
 ** R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)
 ** R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)

- R01DE-05511-02 Evanston-Oak park fluoridation study after 25 years (human)
 ** R23DE-05799-01 Behavioral methods for pedodontic management (human)
 ** R23DE-05858-01 Dentists' behavior and treatment outcomes

DENTAL FILLINGS

- SEE ALSO DENTAL CARIES
 P50DE-02668-15 0191 Regional dental research center - Clinical evaluation of restorative materials and techniques
 R01DE-05761-02 Improved dental instruments and materials
 R01DE-06112-01 Filled sealant as a conservative restorative material (human)

DENTAL FILLINGS, DENTAL INLAYS

- R01DE-04101-07 Corrosion of precious metal alloys (human)
 R23DE-05314-03 Dental alloy corrosion research
 R01DE-05761-02 Improved dental instruments and materials

DENTAL HEALTH (ORAL HEALTH)

SEE ALSO DENTISTRY, PREVENTIVE

SEE ALSO POPULATION SURVEYS, HEALTH SURVEYS, DENTAL

- ** P50DE-02600-15 0034 Support for oral biology research center - Salivary and oral mucosal changes after cancer chemotherapy
 R01DE-04890-03 Plaque control-healing following periodontal surgery
 R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
 ** R01DE-05102-04 Potential anti-carries agents (rats)
 R01DE-05414-02 The local immune response in periodontal disease (human)
 ** R01DE-05511-02 Evanston-Oak park fluoridation study after 25 years (human)
 R01DE-05563-02 The blade implant-Clinical efficacy and safety (human)
 ** R01DE-05684-01 Saliva proteins-Chemistry, genetics and oral health
 R13DE-05752-01 Conference on biology of mineralized connective tissues
 ** R01DE-05999-01 The role of nutrition in oral health
 ** N01DE-92421-14 National caries prevalence survey

DENTAL HEALTH, COMMUNITY DENTAL HEALTH

- R01DE-05596-02 Topically-applied polymers for caries prevention

DENTAL HEALTH EDUCATION

SEE EDUCATION, HEALTH EDUCATION, DENTAL

DENTAL HEALTH SERVICES

- ** R23DE-05497-02 Dental disease and work loss (human)
 ** R23DE-05799-01 Behavioral methods for pedodontic management (human)
 ** R23DE-05858-01 Dentists' behavior and treatment outcomes

DENTAL (HEALTH) SURVEYS

SEE POPULATION SURVEYS, HEALTH SURVEYS, DENTAL

DENTAL IMPLANT (PROSTHETICS)

SEE DENTAL PROSTHESIS, DENTAL IMPLANT

DENTAL IMPLANT ENDOSSEOUS

SEE DENTAL PROSTHESIS, DENTAL IMPLANT ENDOSSEOUS

DENTAL INLAYS

SEE DENTAL FILLINGS, DENTAL INLAYS

DENTAL INSTRUMENTS*

- R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
 ** R01DE-05307-03 Orthodontic treatment with removable appliances (human, monkeys)
 ** R01DE-05761-02 Improved dental instruments and materials

DENTAL INSURANCE

SEE HEALTH INSURANCE, DENTAL

DENTAL MATERIALS

SEE ALSO ORAL-FACIAL RESTORATION MATERIALS

- ** P50DE-02668-15 0149 Regional dental research center - Strengths of polymers in tooth restorative materials
 ** P50DE-02668-15 0150 Regional dental research center - Polymerization of tooth restorative composite materials
 ** P50DE-02668-15 0191 Regional dental research center - Clinical evaluation of restorative materials and techniques
 R01DE-03497-09 Artificial tooth roots (Rhesus monkeys, human)

- ** R01DE-04096-05 Biocompatibility of endodontic materials (animals)
 ** R01DE-04136-07 Maxillofacial materials-Color study
 ** R01DE-05129-04 Improvement of preventive and restorative materials
 ** R01DE-05423-02 Diffuse reflectance by esthetic dental materials
 R01DE-05563-02 The blade implant-Clinical efficacy and safety (human)

- ** R01DE-05761-02 Improved dental instruments and materials
 R13DE-05898-01 13th Annual International Biomaterials Symposium - 1981

DENTAL MATERIALS, AMALGAM DENTAL

- ** R01DE-02320-16 Clinical behavior of dental restorative materials
 P50DE-02668-15 0191 Regional dental research center - Clinical evaluation of restorative materials and techniques

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
 **Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

(contd.)

- ** R01DE-02936-13 Marginal fracture of dental amalgam
- ** R01DE-03601-09 Localized corrosion of dental amalgam
- ** R01DE-03965-08 Dental alloy with small additions of other materials
- ** R01DE-04262-07 Amalgamation kinetics on Ag-Sn (X) alloys
- R01DE-04394-05 Pin and slot retention in amalgam and composite materials
- ** R01DE-04516-03 Corrosion and clinical behavior of dental amalgam
- ** R01DE-04704-05 X-ray and sem analysis of CU rich dental amalgam
- R23DE-05314-03 Dental alloy corrosion research
- ** R01DE-05423-02 Diffuse reflectance by esthetic dental materials
- R01DE-05460-02 Bonding of dental porcelain to non-precious alloys
- R01DE-05761-02 Improved dental instruments and materials
- R01DE-06112-01 Filled sealant as a conservative restorative material (human)

DENTAL MATERIALS, BONDING

SEE ALSO DENTAL MATERIALS, DENTAL ADHESIVES AND SEALANTS

- P50DE-02668-15 0150 Regional dental research center - Polymerization of tooth restorative composite materials
- R01DE-04814-02 New polymers for permanent soft denture liners
- R01DE-04883-04 Nature of alloy systems for crown and bridge restorations (human)
- R01DE-05129-04 Improvement of preventive and restorative materials
- ** R01DE-05460-02 Bonding of dental porcelain to non-precious alloys
- R01DE-05761-02 Improved dental instruments and materials

DENTAL MATERIALS, CASTING

SEE ALSO DENTAL MATERIALS, INVESTMENT

- R01DE-04883-04 Nature of alloy systems for crown and bridge restorations (human)
- R23DE-05314-03 Dental alloy corrosion research
- R01DE-05321-02 Titanium alloys in dentistry
- R23DE-05519-02 Oxidation behavior of Ni-base crown and bridge alloys
- R01DE-05761-02 Improved dental instruments and materials

DENTAL MATERIALS, DENTAL ADHESIVES AND SEALANTS

- R01DE-02320-16 Clinical behavior of dental restorative materials
- R01DE-02525-16 Ultrastructural histopathology of human dental enamel
- P50DE-02731-15 0037 Development support for dental research institute - Luminescence and polarized light in the diagnosis and treatment of caries
- ** R01DE-03713-06 Effect of fissure sealant on progress of dental caries (human)
- ** R01DE-04096-05 Biocompatibility of endodontic materials (animals)
- ** R23DE-05042-03 Assessment of wear of four different sealants in vivo (human)
- R01DE-05761-02 Improved dental instruments and materials
- ** R01DE-05800-01 Formation and biochemical composition of sea mussel
- ** R23DE-05886-01 Organic oligomers for new hydrophobic dental cements
- ** R01DE-06112-01 Filled sealant as a conservative restorative material (human)

DENTAL MATERIALS, DENTAL METALS

SEE ALSO DENTAL MATERIALS, AMALGAM DENTAL

- R01DE-02320-16 Clinical behavior of dental restorative materials
- ** R01DE-04101-07 Corrosion of precious metal alloys (human)
- ** R01DE-04252-07 Semi and nonprecious metal-porcelain systems
- R01DE-04262-07 Amalgamation kinetics on Ag-Sn (X) alloys
- ** R01DE-04394-05 Pin and slot retention in amalgam and composite materials
- ** R01DE-04883-04 Nature of alloy systems for crown and bridge restorations (human)
- ** R23DE-05314-03 Dental alloy corrosion research
- ** R01DE-05321-02 Titanium alloys in dentistry
- ** R01DE-05441-02 Optimization of metal-ceramic restoration design
- ** R01DE-05460-02 Bonding of dental porcelain to non-precious alloys
- ** R23DE-05519-02 Oxidation behavior of Ni-base crown and bridge alloys
- R01DE-05761-02 Improved dental instruments and materials

DENTAL MATERIALS, IMPRESSION MATERIALS

R01DE-05761-02 Improved dental instruments and materials

DENTAL MATERIALS, INVESTMENT

- R01DE-04883-04 Nature of alloy systems for crown and bridge restorations (human)
- R01DE-05761-02 Improved dental instruments and materials

DENTAL MATERIALS, PORCELAINS

- ** R01DE-04252-07 Semi and nonprecious metal-porcelain systems
- R01DE-04883-04 Nature of alloy systems for crown and bridge restorations (human)
- R23DE-05314-03 Dental alloy corrosion research
- ** R01DE-05353-04 Dental porcelains improvement with inorganic polymers

- ** R01DE-05423-02 Diffuse reflectance by esthetic dental materials
- ** R01DE-05441-02 Optimization of metal-ceramic restoration design
- ** R01DE-05460-02 Bonding of dental porcelain to non-precious alloys
- R23DE-05519-02 Oxidation behavior of Ni-base crown and bridge alloys
- R01DE-05761-02 Improved dental instruments and materials

DENTAL MATERIALS, ROOT CANAL FILLING

MATERIALS

- R01DE-04890-03 Plaque control-healing following periodontal surgery
- R01DE-05761-02 Improved dental instruments and materials

DENTAL MATERIALS, WEAR

SEE ALSO DENTAL STRUCTURE, TOOTH WEAR

- P50DE-02668-15 0123 Regional dental research center - In situ replication techniques and the wear of restorative materials
- ** R23DE-05042-03 Assessment of wear of four different sealants in vivo (human)
- R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)
- ** R01DE-05637-01 Mechanical properties of dental composite materials
- R23DE-05945-01 Physicochemical modifications of dental restoratives

DENTAL METALS

SEE DENTAL MATERIALS, DENTAL METALS

DENTAL MOTTILING

SEE DENTAL DISCOLORATION, DENTAL MOTTILING

DENTAL OCCLUSION

SEE ALSO DENTAL DISORDERS, MALOCCLUSION

SEE ALSO DENTISTRY, ORTHODONTICS

- P50DE-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)
- P01DE-02872-12 0038 Craniofacial dysmorphology - Evaluation of craniofacial surgery
- R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
- R01DE-04157-08 Functional mandibular movements (human)
- P50DE-04881-05 0001 Center for clinical research in periodontal diseases - Diagnosis and treatment of destructive periodontal diseases
- ** R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
- ** R01DE-05381-01 Temporomandibular joint changes in young adults
- R01DE-05669-01 Choron type and dental morphology in twins
- R01DE-82413-05 Long-term effect of orthodontic treatment

DENTAL OCCLUSION, BITE AND BITING

STRENGTH (FORCE)

- P01DE-02872-12 0053 Craniofacial dysmorphology - Maxillofacial prosthetics (human)
- ** R01DE-03953-07 Force systems from orthodontic appliances
- R01DE-04047-05 Extensibility characteristics of human cheek
- ** R01DE-04164-06 Functional properties of mammalian masticatory muscles
- ** R01DE-04531-04 Strain in the facial bones of (primates)
- ** R01DE-04610-03 Physiological studies on mastication (human)
- R23DE-05036-03 Nocturnal masseter muscle activity and jaw dysfunction (human)
- R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
- R01DE-05215-03 Influences on stability following orthognathic surgery
- R01DE-05321-02 Titanium alloys in dentistry
- R01DE-05410-02 Orthodontic treatment effects on craniofacial growth (human)
- ** R23DE-05418-03 In vivo forces on endosseous dental implants (dogs)
- R23DE-05627-02 Effects of mechanical forces on craniofacial growth (monkeys, rabbits)

DENTAL PAIN

- P50DE-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)
- ** R01DE-04004-07 Acupuncture and perception of dental pain (human)
- R01DE-04494-05 Control of stress during dental procedures (human)
- ** R01DE-04786-04 Dental and orofacial pain-Brain stem mechanisms (cats)
- ** R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)
- M P01DE-05130-03 Dental/orofacial pain-Mechanisms behavior and modulation
- ** P01DE-05130-03 0006 Dental/orofacial pain-Mechanisms behavior and modulation - Acute pain in research and clinical settings
- ** P01DE-05130-03 0009 Dental/orofacial pain-Mechanisms behavior and modulation - Dental near and far field potentials and pain reactivity (cats, monkeys)
- R23DE-05155-02 Active principles of dental pulp therapeutic agents

- ** R01DE-05159-03 Distribution and ultrastructure of dental innervation (cats, rats)
- ** R01DE-05208-03 Mechanism of dental and facial sensation (monkeys)
- ** R01DE-05369-03 Factors affecting dental postoperative pain
- ** R01DE-05404-03 Dental pain-Trigeminal nucleus caudalis (cats)
- R23DE-05858-01 Dentists' behavior and treatment outcomes
- R23DE-05967-01 Role of prostaglandin E in periodontal disease activity

DENTAL PERSONNEL

- SEE ALSO EDUCATION, HEALTH OCCUPATIONS, DENTAL
- R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)
- R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)
- R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)
- ** R23DE-05858-01 Dentists' behavior and treatment outcomes

DENTAL PHARMACOLOGY

- R01DE-04615-04 Fluoride-cadmium interaction in dental caries (rats, human)
- ** R01DE-04835-03 Anti-carries mechanism of fluoride complexes in vitro (human)
- ** P50DE-04881-05 0004 Center for clinical research in periodontal diseases - Relation of inflammation mediators to destructive periodontal diseases
- ** R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine
- ** R23DE-05155-02 Active principles of dental pulp therapeutic agents
- R01DE-05369-03 Factors affecting dental postoperative pain
- ** R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)
- R23DE-05393-03 Factors association with hyperplasia of oral mucosa

DENTAL PLAQUE

SEE DENTAL DEPOSITS, PLAQUE

DENTAL PLAQUE REMOVAL

SEE DENTAL DEPOSITS REMOVAL

DENTAL PROSTHESIS

SEE ALSO DENTAL FILLINGS

SEE ALSO DENTAL MATERIALS, PORCELAINS

SEE ALSO DENTAL MATERIALS, WEAR

SEE ALSO ORAL-FACIAL RESTORATION, CLEFT PALATE PROSTHESIS

SEE ALSO ORAL-FACIAL RESTORATION, PROSTHODONTICS

- R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)
- P50DE-02668-15 0123 Regional dental research center - In situ replication techniques and the wear of restorative materials
- R01DE-03545-09 Prediction of tooth displacement (human)
- ** R01DE-03631-08 Physiological study of speech adaptation (human)
- R01DE-03713-06 Effect of fissure sealant on progress of dental caries (human)
- ** R01DE-04414-06 Porous high density polyethylene tooth roots (monkeys)
- ** R01DE-04883-04 Nature of alloy systems for crown and bridge restorations (human)
- ** R23DE-05314-03 Dental alloy corrosion research
- R01DE-05441-02 Optimization of metal-ceramic restoration design
- R23DE-05519-02 Oxidation behavior of Ni-base crown and bridge alloys
- ** R01DE-05563-02 The blade implant-Clinical efficacy and safety (human)
- R23DE-05627-02 Effects of mechanical forces on craniofacial growth (monkeys, rabbits)
- ** R23DE-05945-01 Physicochemical modifications of dental restoratives
- ** R01DE-06112-01 Filled sealant as a conservative restorative material (human)

DENTAL PROSTHESIS, DENTAL IMPLANT

- ** R01DE-04394-05 Pin and slot retention in amalgam and composite materials
- ** R13DE-04860-01 Conference-dental implants: benefit or risk
- R01DE-05761-02 Improved dental instruments and materials
- R23DE-05883-01 Implants as anchors to move teeth and facial bones (dogs, monkeys)

DENTAL PROSTHESIS, DENTAL IMPLANT

ENDOSSEOUS

- ** R01DE-03497-09 Artificial tooth roots (Rhesus monkeys, human)
- ** R23DE-05418-03 In vivo forces on endosseous dental implants (dogs)
- ** R01DE-05563-02 The blade implant-Clinical efficacy and safety (human)
- R01DE-05761-02 Improved dental instruments and materials
- R23DE-05883-01 Implants as anchors to move teeth and facial bones (dogs, monkeys)

DENTAL PROSTHESIS, DENTURES

- ** R01DE-02320-16 Clinical behavior of dental restorative materials
- ** R01DE-03953-07 Force systems from orthodontic appliances

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

- ** R01DE-04814-02 New polymers for permanent soft denture liners
R01DE-05321-02 Titanium alloys in dentistry
R01DE-05563-02 The blade implant—Clinical efficacy and safety (human)

DENTAL PULP CALCIFICATION

SEE DENTAL PULP DISORDERS, DENTAL PULP CALCIFICATION

DENTAL PULP DEVITALIZATION (MUMMIFICATION)

SEE DENTISTRY, ENDODONTICS, ROOT CANAL THERAPY

DENTAL PULP DISORDERS

SEE ALSO DENTAL ABSCESS

- R01DE-05137-03 Microscopic and clinical study of cervical erosion
** R23DE-05155-02 Active principles of dental pulp therapeutic agents
** R01DE-05404-03 Dental pain—Trigeminal nucleus caudalis (cats)
R23DE-05605-01 The humoral regulation of pulp circulation (rats)

DENTAL PULP DISORDERS, DENTAL PULP CALCIFICATION

- ** R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

DENTAL PULP OBTURATION

SEE DENTISTRY, ENDODONTICS, ROOT CANAL THERAPY

DENTAL RADIOGRAPHY

SEE DENTAL VISUALIZATION, DENTAL RADIOGRAPHY*

DENTAL RESEARCH*

- ** R01DE-04068-07 Statistical methods in dental research
** R13DE-05752-01 Conference on biology of mineralized connective tissues
R13DE-05753-01 Symposium on host-bacteria in periodontal diseases

DENTAL RESEARCH INSTITUTE REVIEW

COMMITTEE

- M P50DE-02600-15 Support for oral biology research center
M P50DE-02623-14 Center for oral health research
M P50DE-02668-15 Regional dental research center
M P50DE-02670-15 Institute of Dental Research
M P50DE-02731-15 Development support for dental research institute
M P50DE-04881-05 Center for clinical research in periodontal diseases
M P50DE-04898-05 Periodontal disease research center
M P50DE-05139-04 Clinical research center for periodontal disease

DENTAL SEALANTS

SEE DENTAL MATERIALS, DENTAL ADHESIVES AND SEALANTS

DENTAL STRESS ANALYSIS

SEE ALSO DENTAL MATERIALS, WEAR

- R01DE-02936-13 Marginal fracture of dental amalgam
R01DE-05345-09 Prediction of tooth displacement (human)
R01DE-05321-02 Titanium alloys in dentistry

DENTAL STRUCTURE

SEE ALSO ORAL-PHARYNGEAL (REGION)

- ** R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)
R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
** R01DE-05109-02 Composite bone grafts in dentistry and medicine
R01DE-05138-03 Visceral arches and oro-facial morphogenesis (mice, monkeys)
R01DE-05558-01 Sensory alterations of craniofacial form (Rhesus monkeys)
** R01DE-05669-01 Chorion type and dental morphology in twins

DENTAL STRUCTURE, AMELOBLASTS

- ** P50DE-02668-15 0193 Regional dental research center - Metabolism of isolated ameloblasts
P01DE-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)
** R01DE-04230-07 Comparative ultrastructure of mammalian amelogenesis (human, mammals)
R23DE-05062-03 Tissue interactions during odontogenesis
R01DE-05323-02 Calcium transport in developing dental tissues (frogs, rats)
** R23DE-05424-03 Quantitative studies of lysosomes in amelogenesis (rats)
R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
R01DE-05586-01 Cell surface studies of the enamel organ (mice)

DENTAL STRUCTURE, CEMENTUM

- ** P01DE-01850-18 0084 Nutritional sources and metabolic roles of fluoride - Enamel, dentin and cementum in osteogenesis imperfecta (human)
** P50DE-02623-14 0027 Center for oral health research - Collagenase in the periodontium
** P01DE-02847-13 0022 Microbial ecology and its relation to dental disease - Cemental caries as a dental problem (human, rats, primates)
R01DE-03223-11 Kinetics of mineralization of teeth (human)
R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)

- R01DE-05252-01 Bidirectional effects of subgingival dental plaque

DENTAL STRUCTURE, DENTAL ALVEOLUS

- ** P01DE-01850-18 0081 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on strain N mice
** P50DE-02600-15 0028 Support for oral biology research center - Repletion and coupling in bone volume regulation (rat)
P01DE-02872-12 0053 Craniofacial dysmorphism - Maxillofacial prosthetics (human)
R01DE-03545-09 Prediction of tooth displacement (human)
R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)
R01DE-04039-04 Sex steroid metabolism in oral tissues
** R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)
R01DE-05078-05 Craniofacial growth and remodeling (human)
R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)
R01DE-05255-03 Regulation of collagenase and bone resorption (chick embryos, mice)
R01DE-05413-02 Bone resorption in periodontal disease
R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
** R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
** R01DE-06065-01 The role of lymphoid cells in alveolar bone resorption

DENTAL STRUCTURE, DENTIN

- ** R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
** P01DE-01850-18 0084 Nutritional sources and metabolic roles of fluoride - Enamel, dentin and cementum in osteogenesis imperfecta (human)
** R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
P50DE-02668-15 0125 Regional dental research center - Collagen crosslinks and the fate of extracellular matrix
P50DE-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues
P50DE-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions
R01DE-03223-11 Kinetics of mineralization of teeth (human)
R01DE-03713-06 Effect of fissure sealant on progress of dental caries (human)
** R01DE-03780-09 Permeability characteristics of dentin (dogs, human)
R01DE-03856-07 Fluoride-selenium interaction in dental caries (rats)
R01DE-04394-05 Pin and slot retention in amalgam and composite materials
R01DE-04616-04 Fluoride-cadmium interaction in dental caries (rats)
R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
R01DE-05092-03 Proteins involved in dentinogenesis
R01DE-05137-03 Microscopic and clinical study of cervical erosion
R23DE-05155-02 Active principles of dental pulp therapeutic agents
R01DE-05323-02 Calcium transport in developing dental tissues (frogs, rats)
R01DE-05351-02 Electron optical examination of mineralized tissues (animals)
** R01DE-05483-02 Characterization of predentin extracellular fluid (rats)
R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
** R01DE-05530-01 Internal structure of dentine (human, rats)
** R13DE-05752-01 Conference on biology of mineralized connective tissues

DENTAL STRUCTURE, ENAMEL

- ** R01DE-01830-19 Quantitation of enamel demineralization mechanisms
** P01DE-01850-18 0084 Nutritional sources and metabolic roles of fluoride - Enamel, dentin and cementum in osteogenesis imperfecta (human)
** R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
** R01DE-02525-16 Ultrastructural histopathology of human dental enamel
** P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel
P50DE-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions
P50DE-02670-15 0020 Institute of Dental Research - Nutrition—Disease proneness during dental development
** P50DE-02670-15 0036 Institute of Dental Research - Varnish and trace elements effects on enamel fluoride and dental caries (rats)
** P50DE-02731-15 0036 Development support for dental research institute - Optimal methods of enamel remineralization
P01DE-02847-13 0021 Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)

- P01DE-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)
** R01DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)
R01DE-03223-11 Kinetics of mineralization of teeth (human)
R01DE-03856-07 Fluoride-selenium interaction in dental caries (rats)
R01DE-03915-08 Tooth-saliva interface phenomena and dental caries (rabbits, goats)
R01DE-04192-07 SnF₂-Ca (OH) 2-H₃O₄-H₂O reaction system
** R01DE-04230-07 Comparative ultrastructure of mammalian amelogenesis (human, mammals)
R01DE-04385-06 Mechanism of dental caries (human)
R01DE-04394-05 Pin and slot retention in amalgam and composite materials
R01DE-04486-04 Kinetics and mechanisms of action of fluorides
R01DE-04529-05 Replacement therapy of dental caries (rats, monkeys)
R01DE-04600-04 Hydroxyapatite remineralization—Role of fluoride
R01DE-04616-04 Fluoride-cadmium interaction in dental caries (rats)
R01DE-04705-03 Reactions of titanium fluoride with hydroxyapatite
** R01DE-04819-05 Remineralization of enamel caries in vitro (human)
R01DE-04835-03 Anti-carries mechanism of fluoride complexes in vitro (human)
R23DE-05037-03 Biochemical role of zinc in teeth and bones
** R01DE-05224-01 Enamel silylation as a caries prevention method (human, animals)
** R01DE-05289-03 Fluorine ion binding by early enamel matrix proteins (rats)
R01DE-05351-02 Electron optical examination of mineralized tissues (animals)
R01DE-05354-04 Prevention of dental caries (rats, human)
R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
R23DE-05491-02 Control of biomineralization in two species (snails)
R01DE-05510-02 Physico-chemistry of strontium in caries lesions
R01DE-05596-02 Topically-applied polymers for caries prevention
R01DE-05690-01 Localization of the procollagens in dental tissues
R01DE-05773-01 Ligand receptor interactions of cariogenic bacteria
R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
R01DE-06113-01 Determinants of fluoride in the oral environment (Dogs, rats)
** R01DE-12432-00 Caries and enamel fluoride

DENTAL STRUCTURE, ENAMEL ORGAN

SEE ALSO DENTAL STRUCTURE, AMELOBLASTS

- R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)
R01DE-05323-02 Calcium transport in developing dental tissues (frogs, rats)
R23DE-05424-03 Quantitative studies of lysosomes in amelogenesis (rats)
** R01DE-05586-01 Cell surface studies of the enamel organ (mice)
R23DE-05749-01 Salivary proline-rich proteins—Localization/secretion (monkeys)

DENTAL STRUCTURE, GINGIVA

- R01DE-01554-20 Host factors in caries resistance (human, rats)
R01DE-02320-16 Clinical behavior of dental restorative materials
P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
P50DE-02600-15 0032 Support for oral biology research center - Keratohyalin in keratinization of oral mucosa and skin (human, rats)
** R01DE-03301-11 Connective tissue of the periodontium—Collagen maturation
R01DE-03318-10 The molecular nature of gingival and mucosal collagen (rat)
** R01DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)
R01DE-04039-04 Sex steroid metabolism in oral tissues
** R01DE-04125-06 Gingival matrix proteins and periodontal disease (human, mammals)
R01DE-04660-06 Keratohyalin in keratinization—Oral mucosa and skin (human)
R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)
R01DE-05640-01 Cytotoxicity of periodontopathic bacteria
** R01DE-05817-01 Gingival collagenase—Quantitation and localization (rabbits, mice, human)
** R01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects. See Appendix for investigator's name and Grant Number.

(contd.)

DENTAL STRUCTURE, GINGIVA, GINGIVAL**SULCUS**

- R01DE-03488-10 Microbial composition of developing dental plaque
- R01DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)
- R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- R23DE-05050-02 Sources of toxins from human dental plaque
- R01DE-05104-02 Periodontitis--Microbial etiology and prediction
- R01DE-05252-01 Bidirectional effects of subgingival dental plaque
- R23DE-05429-03 Adherence of periodontal disease-associated bacteria
- R23DE-05599-02 Microbiology of ligature-induced periodontitis
- R01DE-05817-01 Gingival collagenase--Quantitation and localization (rabbits, mice, human)
- R23DE-05967-01 Role of prostaglandin E in periodontal disease activity

DENTAL STRUCTURE, ODONTOBLASTS

- P50DE-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues
- P01DE-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)
- R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
- R23DE-05062-03 Tissue interactions during odontogenesis
- R01DE-05092-03 Proteins involved in dentinogenesis
- R01DE-05159-03 Distribution and ultrastructure of dental innervation (cats, rats)
- R01DE-05323-02 Calcium transport in developing dental tissues (frogs, rats)
- R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
- R01DE-05530-01 Internal structure of dentine (human, rats)
- R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

DENTAL STRUCTURE, PERIODONTIUM

- P50DE-02623-14 0026 Center for oral health research - Collagen biosynthesis in the periodontium
- P50DE-02623-14 0027 Center for oral health research - Collagenase in the periodontium
- P50DE-02731-15 0033 Development support for dental research institute - Clinical trials of periodontal therapy
- R01DE-03301-11 Connective tissue of the periodontium--Collagen maturation
- R01DE-03545-09 Prediction of tooth displacement (human)
- R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)
- R01DE-04844-04 Stress-related bone resorption--Mechanisms of action (rats)
- P50DE-04898-05 0004 Periodontal disease research center - Periodontal disease and the electromyographic silent period (human)
- R01DE-05078-05 Craniofacial growth and remodeling (human)
- R01DE-05109-02 Composite bone grafts in dentistry and medicine
- R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
- R01DE-05159-03 Distribution and ultrastructure of dental innervation (cats, rats)
- R01DE-05495-02 Myofibroblast contraction in periodontium (rats)

DENTAL STRUCTURE, PULP**SEE ALSO DENTISTRY, ENDODONTICS**

- R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)
- R01DE-04335-05 Comparison of treatment procedures used in endodontics
- R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)
- R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)
- R23DE-05605-01 The humoral regulation of pulp circulation (rats)
- R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

DENTAL STRUCTURE, PULP FLUID

- R01DE-03780-09 Permeability characteristics of dentin (dogs, human)

DENTAL STRUCTURE, TOOTH**SEE ALSO CONGENITAL ABNORMALITIES, DENTITION**

- R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)
- P50DE-02623-14 0009 Center for oral health research - Oral microorganisms in periodontal health and disease (human, rats)
- P50DE-02658-15 0123 Regional dental research center - In situ replication techniques and the wear of restorative materials
- P01DE-02847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
- R01DE-03545-09 Prediction of tooth displacement (human)
- R01DE-03915-08 Tooth-saliva interface phenomena and dental caries (rabbits, goats)

- R01DE-04141-07 Mechanism of hard tissue mineralization (human, rats)
- R01DE-04345-06 Cellular and molecular aspects of mineralization (chick embryo)
- R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
- R23DE-05062-03 Tissue interactions during odontogenesis
- R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)
- R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
- R01DE-05769-03 Ultrastructure of tooth development
- R01DE-05832-01 Organization of the trigeminal mesencephalic nucleus (monkeys, opossums)

DENTAL STRUCTURE, TOOTH GERM

- R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine

DENTAL STRUCTURE, TOOTH MOBILITY

- R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)
- R01DE-03953-07 Force systems from orthodontic appliances
- R01DE-04047-05 Extensibility characteristics of human cheek
- R01DE-04487-05 Pulsating forces in orthodontics (human)
- R01DE-04844-04 Stress-related bone resorption--Mechanisms of action (rats)
- R01DE-05412-02 Electric current, bone remodeling and tooth movement (cats)
- R01DE-05495-02 Myofibroblast contraction in periodontium (rats)
- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
- R23DE-05883-01 Implants as anchors to move teeth and facial bones (dogs, monkeys)

DENTAL STRUCTURE, TOOTH ROOT**SEE ALSO DENTISTRY, ENDODONTICS**

- P50DE-02623-14 0005 Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- P50DE-02623-14 0027 Center for oral health research - Collagenase in the periodontium
- P01DE-02847-13 0022 Microbial ecology and its relation to dental disease - Cemental caries as a dental problem (human, rats, primates)
- R01DE-03497-09 Artificial tooth roots (Rhesus monkeys, human)
- R01DE-04414-06 Porous high density polyethylene tooth roots (monkeys)
- R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
- R01DE-05996-01 Alveolar bone metabolism during tooth eruption (Dogs)

DENTAL STRUCTURE, TOOTH WEAR**SEE ALSO DENTISTRY, BRUXISM****SEE ALSO DENTISTRY, MASTICATION**

- R01DE-04414-06 Porous high density polyethylene tooth roots (monkeys)
- R01DE-05137-03 Microscopic and clinical study of cervical erosion

DENTAL STUDY SECTION**SEE ORAL BIOLOGY AND MEDICINE STUDY SECTION****DENTAL TRANSPLANTATION**

- R01DE-03545-09 Prediction of tooth displacement (human)
- R01DE-04489-06 Tooth transplantation genetics and immunology (mice, monkeys)
- R23DE-05897-01 Oral immunogenetics and tissue transplantation (symposium)

DENTAL VISUALIZATION*

- R01DE-04157-08 Functional mandibular movements (human)

DENTAL VISUALIZATION, DENTAL**RADIOGRAPHY***

- R01DE-03598-07 Dentofacial effects of forces to retract the maxilla (human)
- R01DE-04783-04 The development of a dental x-ray aiming device

DENTIFRICES

- R01DE-12431-00 dentifrice
- R01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)

DENTIN**SEE DENTAL STRUCTURE, DENTIN****DENTIN SENSITIVITY****SEE DENTAL PAIN****DENTINOGENESIS****SEE DENTAL DEVELOPMENT, DENTINOGENESIS****DENTISTRY****SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL****SEE ALSO ORAL-FACIAL RESTORATION****SEE ALSO ORAL-PHARYNGEAL, JAW****SEE ALSO ORAL SURGERY****SEE ALSO SENSORY DEPRESSION, ANESTHESIA DENTAL**

- R01DE-03568-07 0013 Craniofacial anomalies--Etiology and treatment -
- R01DE-04494-05 Control of stress during dental procedures (human)

- R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)
- R01DE-05636-01 Cellular mediators in tooth maintenance and repair (human)
- R01DE-05904-01 Revision of the F.D.I dental lexicon

DENTISTRY, BRUXISM

- P50DE-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)
- R01DE-04889-04 Dental significance of jaw muscle silent periods (human)
- R23DE-05036-03 Nocturnal masseter muscle activity and jaw dysfunction (human)
- R23DE-05527-02 Behavioral treatments for nocturnal bruxism (human)

DENTISTRY, ENDODONTICS**SEE ALSO DENTAL STRUCTURE, PULP****SEE ALSO DENTAL STRUCTURE, TOOTH ROOT**

- R01DE-04096-05 Biocompatibility of endodontic materials (animals)
- R01DE-04335-05 Comparison of treatment procedures used in endodontics
- R01DE-04414-06 Porous high density polyethylene tooth roots (monkeys)

DENTISTRY, ENDODONTICS, PULPOTOMY

- R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)

DENTISTRY, ENDODONTICS, ROOT CANAL THERAPY

- R01DE-04335-05 Comparison of treatment procedures used in endodontics

DENTISTRY, MASTICATION**SEE ALSO ORAL-PHARYNGEAL, JAW MOVEMENT**

- P50DE-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)
- P01DE-02872-12 0038 Craniofacial dysmorphology - Evaluation of craniofacial surgery
- R01DE-03794-09 Surgical-orthodontics and bone healing (monkeys)
- R01DE-04157-08 Functional mandibular movements (human)
- R01DE-04164-06 Functional properties of mammalian masticatory muscles
- R01DE-04227-07 Adaptations to changes in masticatory muscle length (monkeys)
- R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate
- R01DE-04531-04 Strain in the facial bones of (primates)
- R01DE-04610-03 Physiological studies on mastication (human)
- R01DE-04884-13 Neural processes in somatic movement (monkeys)
- R01DE-04889-04 Dental significance of jaw muscle silent periods (human)
- R01DE-04940-04 Muscular disorders in craniofacial malformations (human)
- R01DE-05112-03 Muscle activity and control in mastication (mammals, lizards)
- R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
- R23DE-05232-03 Growth and function of the muscles of mastication (monkeys)
- R23DE-05310-03 Neural control of mandibular movement
- R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)
- R23DE-05418-03 In vivo forces on endosseous dental implants (dogs)
- R01DE-05738-01 Mastication, food transport, and swallowing in primates
- R01DE-05832-01 Organization of the trigeminal mesencephalic nucleus (monkeys, opossums)
- R01DE-06000-01 Effect of parotid function on saliva and cells

DENTISTRY, ORTHODONTICS**SEE ALSO DENTAL DISORDERS, MALOCCLUSION****SEE ALSO DENTAL OCCLUSION**

- R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
- R01DE-03545-09 Prediction of tooth displacement (human)
- R01DE-03598-07 Dentofacial effects of forces to retract the maxilla (human)
- R01DE-03794-09 Surgical-orthodontics and bone healing (monkeys)
- R01DE-03953-07 Force systems from orthodontic appliances
- R01DE-04047-05 Extensibility characteristics of human cheek
- R01DE-04157-08 Functional mandibular movements (human)
- R01DE-04487-05 Pulsating forces in orthodontics (human)
- R01DE-04844-04 Stress-related bone resorption--Mechanisms of action (rats)
- R01DE-04990-03 Normal and abnormal faces (human)
- R01DE-05203-03 Speech adaptations to orthognathic surgery (human)
- R01DE-05307-03 Orthodontic treatment with removable appliances (human, monkeys)
- R01DE-05321-02 Titanium alloys in dentistry
- R01DE-05410-02 Orthodontic treatment effects on craniofacial growth (human)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects. See Appendix for investigator's name and Grant Number.

- R01DE-05412-02 Electric current, bone remodeling and tooth movement (cats)
- ** R13DE-05468-01 Symposium on orthodontics and bioengineering (Connecticut)
- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
- R23DE-05883-01 Implants as anchors to move teeth and facial bones (dogs, monkeys)
- ** N01DE-82413-05 Long-term effect of orthodontic treatment

DENTISTRY, PREVENTIVE

- SEE ALSO DENTAL CARIES INHIBITORS
- SEE ALSO DENTAL DEPOSITS REMOVAL
- SEE ALSO DENTAL DISORDERS CHEMOTHERAPY, FLUORIDE INGESTED
- SEE ALSO DENTAL DISORDERS CHEMOTHERAPY, FLUORIDE TREATMENTS (TOPICAL)
- SEE ALSO VACCINES, BACTERIAL, ANTI-CARIES VACCINE
- R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
- ** N01DE-02427-04 Synthesize noncariogenic sweeteners
- ** N01DE-02428-04 Synthesis of noncariogenic sweeteners (mice)
- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- P50DE-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions
- P50DE-02570-15 0035 Institute of Dental Research - Granulocyte growth and division
- P50DE-02670-15 0036 Institute of Dental Research - Varnish and trace elements effects on enamel fluoride and dental caries (rats)
- ** R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)
- R01DE-03654-09 Molecular basis of dental caries (human)
- R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)
- R01DE-04385-06 Mechanism of dental caries (human)
- R01DE-04486-04 Kinetics and mechanisms of action of fluorides
- R01DE-04501-06 Cell mediated immunity in gingival inflammation (mice)
- R01DE-04504-03 Plaque bacteria as predictors of human dental caries
- R01DE-04835-03 Anti-caries mechanism of fluoride complexes in vitro (human)
- ** P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
- R01DE-05017-03 Characterization of surface antigens of S mutants
- R23DE-05042-03 Assessment of wear of four different sealants in vivo (human)
- ** R01DE-05129-04 Improvement of preventive and restorative materials
- R01DE-05137-03 Microscopic and clinical study of cervical erosion
- R01DE-05224-01 Enamel silylation as a caries prevention method (human, animals)
- R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)
- ** R01DE-05354-04 Prevention of dental caries (rats, human)
- R23DE-05429-03 Adherence of periodontal disease-associated bacteria
- ** R01DE-05476-02 Novel peptide derived sweeteners
- R01DE-05494-02 Activation of macrophages in periodontal disease
- ** R23DE-05497-02 Dental disease and work loss (human)
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05510-02 Physico-chemistry of strontium in caries lesions
- ** R01DE-05596-02 Topically-applied polymers for caries prevention
- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
- ** N01DE-62491-12 Use of mutants of cariogenic streptococci to prevent dental caries (rats)
- ** N01DE-72407-07 Effect of tooth-cleaning on sodium fluoride rinse
- ** N01DE-92419-02 Efficacy of prior toothcleaning on fluoride treatment

DENTISTRY, PREVENTIVE, TOOTH BRUSHING

- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- R23DE-05393-03 Factors association with hyperplasia of oral mucosa
- N01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)

DENTISTRY, SUBGINGIVAL CURETTAGE

- R01DE-05252-01 Bidirectional effects of subgingival dental plaque
- N01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)

DENTITION DISORDERS, CONGENITAL

SEE CONGENITAL ABNORMALITIES, DENTITION

DENTURES

SEE DENTAL PROSTHESIS, DENTURES

DEOXYHEXOSSES

SEE HEXOSSES, DEOXYHEXOSSES

11-DEOXY-17-HYDROXYCORTICOSTERONE

SEE ADRENAL CORTEX HORMONES, 11-DEOXY-17-HYDROXYCORTICOSTERONE

DEOXYRIBONUCLEASE

SEE NUCLEASES, DEOXYRIBONUCLEASE

DEOXYRIBONUCLEASE 5'-OLIGONUCLEOTIDYLHYDROLASE

SEE NUCLEASES, DEOXYRIBONUCLEASE

DEOXYRIBONUCLEIC ACID(S)

SEE NUCLEIC ACIDS, DNA

DEOXYRIBONUCLEIC ACID(S) REPLICATION

SEE NUCLEIC ACIDS SYNTHESIS, DNA

DEPOLYMERIZATION

SEE MOLECULAR CONDENSATIONS, POLYMERIZATION-DEPOLYMERIZATION

DESENSITIZATION PSYCHOTHERAPY

SEE PSYCHOTHERAPY, DESENSITIZATION

DESIGN OF BIOMATERIALS

SEE BIOMATERIALS, DEVELOPMENT AND PREPARATION OF BIOMATERIALS

DESMOSOMES

SEE CELL-CELL INTERACTION, INTERCELLULAR CONNECTIONS-JUNCTIONS

DETOXICATION

SEE TOXICOLOGY, TOXICANT METABOLISM, DETOXICATION

DEVELOPMENT

SEE CELL DIFFERENTIATION

SEE CHILD DEVELOPMENT (NON-PSYCHOLOGICAL)

SEE CHILD MENTAL DEVELOPMENT

SEE EMBRYOLOGY

SEE GROWTH AND DEVELOPMENT

DEVELOPMENT OF BIOMATERIALS

SEE BIOMATERIALS, DEVELOPMENT AND PREPARATION OF BIOMATERIALS

DEVELOPMENT OF DRUGS

SEE DRUGS SYNTHESIS, DESIGN AND PRODUCTION

DEVELOPMENTAL DISORDERS (INTRAUTERINE FAILURE TO THRIVE)

SEE PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)

DEVELOPMENTAL GENETICS

SEE GENETICS, DEVELOPMENTAL GENETICS

DEVELOPMENTAL NEUROLOGY

SEE NEUROLOGY, DEVELOPMENTAL

DEVELOPMENTAL NUTRITION (GENERAL)

SEE NUTRITION, DEVELOPMENTAL NUTRITION

DEVELOPMENTAL PHARMACOLOGY (DRUG ADVERSE EFFECTS FETAL)

SEE PREGNANCY, EMBRYO-FETUS DRUGS ADVERSE EFFECTS

DEVELOPMENTAL PSYCHOLOGY (CHILD MENTAL DEVELOPMENT)

SEE CHILD MENTAL DEVELOPMENT

DEXTRAN

SEE HEXOSANS, GLUCANS, DEXTRAN

DEXTRINS

SEE HEXOSANS, GLUCANS, DEXTRINS

DIABETES (INCLUDING NON-INBORN CASES)

SEE CARBOHYDRATES METABOLISM DISORDERS, DIABETES

DIABETES, JUVENILE

SEE CARBOHYDRATES METABOLISM DISORDERS, DIABETES, INSULIN-DEPENDENT DIABETES

DIABETES MELLITUS

SEE CARBOHYDRATES METABOLISM DISORDERS, DIABETES

DIABETES PHOSPHATE

SEE METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN

DIABETES THERAPY

SEE CARBOHYDRATES METABOLISM DISORDERS, DIABETES THERAPY

DIAGNOSTIC TESTS, EARLY DIAGNOSIS*

P50DE-02731-15 0037 Development support for dental research institute - Luminescence and polarized light in the diagnosis and treatment of caries

R01DE-05550-01 Rapid identification of oral bacteria

DIAGNOSTIC TESTS, NON-INVASIVE*

R01DE-03545-09 Prediction of tooth displacement (human)

DIAMINO ACIDS, ARGININE

P50DE-02600-15 0040 Support for oral biology research center - Fate of actinomycetes viscosus components within phagocytic cells

P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin

R01DE-03993-07 Effect of saliva on the metabolism of dental plaque

DIAMINO ACIDS, LYSINE

P50DE-02568-15 0190 Regional dental research center - Thrombin and prothrombin

DIAMINO ACIDS, ORNITHINE

P50DE-02600-15 0040 Support for oral biology research center - Fate of actinomycetes viscosus components within phagocytic cells

DIASTASES

SEE CARBOHYDRASES, AMYLASE

DIAZEPAM

SEE AZEPINES, DIAZEPINES, DIAZEPAM

DIAZINODIAZINES, DIPYRIDAMOLE

R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)

DIBENZANTHRENES

SEE CYCLICS, CARBOPOLYCYCLICS, BENZANTHRACENES

DICARBOXYLIC AMINO ACIDS, ASPARTIC ACID

R01DE-05476-02 Novel peptide derived sweeteners

DICARBOXYLIC AMINO ACIDS, GLUTAMATES

R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)

DIET

SEE NUTRITION, DIET

DIET PATHOGENIC

SEE NUTRITION, DIET PATHOGENIC

DIETARY CALCIUM

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY CALCIUM

DIETARY CARBOHYDRATES

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY CARBOHYDRATES

DIETARY CONSTITUENTS

SEE NUTRITION, DIETARY CONSTITUENTS (GENERAL)

SEE NUTRITION, DIETETICS

DIETARY DEFICIENCY

SEE NUTRITIONAL ABNORMALITIES, MALNUTRITION (GENERAL)

DIETARY IRON

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY IRON

DIETARY LIPIDS

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY LIPIDS

DIETARY METALS

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY TRACE ELEMENTS AND MINERALS

DIETARY MINERALS

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY TRACE ELEMENTS AND MINERALS

DIETARY NUTRIENTS, GASTROINTESTINAL ABSORPTION

SEE GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT, DIETARY NUTRIENTS

DIETARY PROTEINS

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY PROTEINS

DIETARY REQUIREMENTS

SEE NUTRITIONAL REQUIREMENTS

DIETARY SALTS

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY SALTS

DIETARY SUGARS

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY CARBOHYDRATES

DIETARY SUPPLEMENTS

SEE NUTRITIONAL REQUIREMENTS, DIETARY SUPPLEMENTS

DIETARY SWEETENERS, ARTIFICIAL

SEE FOOD, SWEETENING AGENTS

DIETARY TRACE ELEMENTS AND MINERALS

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY TRACE ELEMENTS AND MINERALS

DIETETICS

SEE NUTRITION, DIETETICS

DIFFERENTIATION

SEE CELL DIFFERENTIATION

SEE GROWTH AND DEVELOPMENT, HISTOGENESIS

DIFFUSION

SEE BIOLOGICAL TRANSPORT, PASSIVE TRANSPORT, DIFFUSION

SEE PHYSICAL PROPERTIES, DIFFUSION

DIFFUSION HORMONES

SEE NEUROTRANSMITTERS AND NEUROMODULATORS (GENERAL)

DIGESTANTS (GENERAL)

SEE GASTROINTESTINAL AGENTS, DIGESTANTS (GENERAL)

DIGESTIVE SYSTEM

SEE GASTROINTESTINAL SYSTEM (GENERAL)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

DIGLYCERIDES

SEE LIPIDS, GLYCERIDES, DIGLYCERIDES

1,25-DIHYDROXYCHOLECALCIFEROL

SEE VITAMIN D GROUP, VITAMIN D3 ACTIVATED

DIHYDROXYPHENYLALANINE

SEE CYCLIC AMINO ACIDS, DOPA

DILANTIN

SEE IMIDAZOLEIDONES, HYDANTOINS, DIPHENYLHYDANTOIN

DIMETHYLBENZANTHRACENES

SEE CYCLICS, CARBOPOLYCYCLICS, BENZANTHRACENES

1,3-DIMETHYLXANTHINE

SEE PURINES, XANTHINES, THEOPHYLLINE

DIMORPHISM; POLYMORPHISM (BIOLOGY)

SEE BIOLOGY, POLYMORPHISM

DIPHENYLHYDANTOIN

SEE IMIDAZOLEIDONES, HYDANTOINS, DIPHENYLHYDANTOIN

DIPHOSPHOGLYCERATES

SEE TRIOSE ACIDS, GLYCERIC ACID DIPHOSPHATES

DIPHOSPHONATES

SEE PHOSPHONATES, DIPHOSPHONATES

DIPHOTHEROIDS

SEE BACTERIA, CORYNEFORM GROUP, CORYNEBACTERIUM*

DIPYRIDAMOLE

SEE DIAZINDOAZINES, DIPYRIDAMOLE

DISABLED CHILDREN

SEE CHILDRN, HANDICAPPED CHILDREN

DISACCHARIDES, LACTOSE

N01DE-12434-00 Identify cariogenic elements of food

DISACCHARIDES, MALTOSE

N01DE-02427-04 Synthesize noncariogenic sweeteners

DISACCHARIDES, SUCROSE

N01DE-02427-04 Synthesize noncariogenic sweeteners

** N01DE-02428-04 Synthesis of noncariogenic sweeteners (mice)

** P01DE-02847-13 002t Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)

R01DE-03258-10 Streptococcus mutans--Dental caries mechanism (human)

R01DE-03654-09 Molecular basis of dental caries (human)

R01DE-03739-09 Glycosyltransferases from oral bacteria (bacteria)

R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)

R01DE-04795-05 Characteristics of cariogenic dental plaque

R01DE-05102-04 Potential anti-caries agents (rats)

N01DE-12434-00 Identify cariogenic elements of food

DISEASE CLASSIFICATION

SEE ALSO NEOPLASMS CLASSIFICATION AND STAGING

** P01DE-02872-12 0055 Craniofacial dysmorphology - Human genetics

R01DE-05054-03 Periodontal diseases--Microbiological studies

R01DE-05104-02 Periodontitis--Microbial etiology and prediction

DISEASE CONTROL AND EPIDEMIOLOGY**STUDY SECTION**

SEE EPIDEMIOLOGY AND DISEASE CONTROL STUDY SECTION

DISEASE CONTROL, COMMUNICABLE**(INFECTIOUS) DISEASES**

SEE COMMUNICABLE DISEASE CONTROL

DISEASE PREVENTION AND CONTROL

SEE HEALTH, DISEASE PREVENTION AND CONTROL

DISEASE PRONENESS-RISK

SEE ALSO POPULATION STUDIES HUMAN, EPIDEMIOLOGY

R01DE-01554-20 Host factors in caries resistance (human, rats)

** P50DE-02668-15 0212 Regional dental research center - Determination of risk related to alcohol consumption before pregnancy recognition

** P50DE-02670-15 0020 Institute of Dental Research - Nutrition--Disease proneness during dental development

** P01DE-02848-11 0002 Biology of connective tissue, bones, and teeth - Steroid receptors in craniofacial teratology (mice)

** R01DE-04504-03 Plaque bacteria as predictors of human dental caries

R01DE-05104-02 Periodontitis--Microbial etiology and prediction

R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

R01DE-05168-03 Glucocorticoid receptors and cleft palate (mice)

R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)

DISEASE REGISTRIES (CLINICAL DISEASE)

SEE HEALTH RECORD SYSTEMS, PATIENT (DISEASE) REGISTRIES

DISEASES, ACUTE (GENERAL)

** P01DE-05130-03 0006 Dental/orofacial pain--Mechanisms behavior and modulation - Acute pain in research and clinical settings

DISEASES, CHRONIC (GENERAL)

SEE ALSO BACTERIAL DISEASES

SEE ALSO BRAIN DISORDERS, EPILEPSY

SEE ALSO CARBOHYDRATES METABOLISM DISORDERS, DIABETES

SEE ALSO CONNECTIVE TISSUE DISORDERS, COLLAGEN DISEASES

SEE ALSO CONNECTIVE TISSUE DISORDERS, LUPUS

ERYTHEMATOSUS SYSTEMIC

SEE ALSO IMMUNOPATHOLOGY, IMMUNOLOGIC DEFICIENCY DISORDERS

SEE ALSO METABOLIC DISORDERS INBORN

SEE ALSO SKELETAL DISORDERS, ARTHRITIS

SEE ALSO VIRUS DISEASE CHARACTERISTICS, LATENT DORMANT OR SLOW

P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)

R01DE-05104-02 Periodontitis--Microbial etiology and prediction

R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)

R01DE-05413-02 Bone resorption in periodontal disease

R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

R01DE-05626-01 Role of complement in periodontal disease

R130E-05753-01 Symposium on host-bacteria in periodontal diseases

** R130E-05982-01 Third World Congress on Pain (Scotland)

DISEASES, COMPLICATIONS

P01DE-01850-18 0081 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on strain N mice

DISEASES, COMPLICATIONS, ANESTHESIA RELATED

R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

DISEASES, COMPLICATIONS, POSTOPERATIVE

R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

** R01DE-05369-03 Factors affecting dental postoperative pain

DISEASES, PATHOLOGIC PROCESSES (NOT CLASSIFIED ELSEWHERE)

R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations

R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)

** R23DE-05599-02 Microbiology of ligature-induced periodontitis

DISEASES, PATHOLOGIC PROCESSES, AUTOLYSIS

R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)

DISEASES, PATHOLOGIC PROCESSES, INFLAMMATION

R01DE-02320-16 Clinical behavior of dental restorative materials

P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)

P50DE-02600-15 0032 Support for oral biology research center - Keratohyalin in keratinization of oral mucosa and skin (human, rats)

P50DE-02623-14 0023 Center for oral health research - Interactions of oral bacteria and polymorphonuclear leukocytes

P50DE-02623-14 0026 Center for oral health research - Collagen biosynthesis in the periodontium

** R01DE-03318-10 The molecular nature of gingival and mucosal collagen (rat)

** R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)

R01DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)

R01DE-04096-05 Biocompatibility of endodontic materials (animals)

** R01DE-04501-06 Cell mediated immunity in gingival inflammation (mice)

P50DE-04881-05 0001 Center for clinical research in periodontal diseases - Diagnosis and treatment of destructive periodontal diseases

P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations

R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)

R23DE-05332-03 Bone in vitro--Ultrastructure and autoradiography (mice)

R01DE-05413-02 Bone resorption in periodontal disease

R01DE-05414-02 The local immune response in periodontal disease (human)

R01DE-05494-02 Activation of macrophages in periodontal disease

R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

R01DE-05512-02 Role of macrophages in periodontal disease

R01DE-05525-02 Nature of the permeability barrier in oral epithelium

R01DE-05626-01 Role of complement in periodontal disease

** R23DE-05793-01 Degradation of collagen in inflammation (human gingiva)

R01DE-05817-01 Gingival collagenase--Quantitation and localization (rabbits, mice, human)

R23DE-05883-01 Implants as anchors to move teeth and facial bones (dogs, monkeys)

R23DE-05967-01 Role of prostaglandin E in periodontal disease activity

DISEASES, PATHOLOGIC PROCESSES, INFLAMMATION, ANTINFLAMMATORY AGENTS

** P50DE-04881-05 0004 Center for clinical research in periodontal diseases - Relation of inflammation mediators to destructive periodontal diseases

R23DE-05393-03 Factors association with hyperplasia of oral mucosa

R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)

DISEASES, PROGNOSIS

R01DE-04504-03 Plaque bacteria as predictors of human dental caries

R01DE-05330-02 Herpes virus antibodies in patients with oral cancer

P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)

DISPLEASURE

SEE PSYCHOLOGY, EMOTIONS, PLEASURE-DISPLEASURE (GENERAL)

DISSECTION

SEE SURGERY, MICROSURGERY AND MICRODISSECTION

DISULFIDE BONDS

SEE CHEMICAL BONDS, DISULFIDE BONDS

DISULFIDES

SEE SULFIDES, DISULFIDES

DIURNAL VARIATION

SEE BIOPERIODICITY, CIRCADIAN RHYTHMS

DL-A LOCUS (DOG)

SEE IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)

DNA

SEE NUCLEIC ACIDS, DNA

DNA, RECOMBINANT, ARTIFICIALLY INDUCED

SEE GENETIC MANIPULATION

DNA BACTERIAL

SEE NUCLEIC ACIDS, DNA BACTERIAL

DNA BIOSYNTHESIS

SEE NUCLEIC ACIDS SYNTHESIS, DNA

DNA CLONING

SEE NUCLEIC ACIDS CLONING

DNA LIGASE (REPAIRASE)

SEE NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)

DNA MANIPULATION (TRANSFER TO FOREIGN HOSTS)

SEE GENETIC MANIPULATION

DNA REPAIR (ENZYMES)

SEE NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)

DNA REPLICATION

SEE NUCLEIC ACIDS SYNTHESIS, DNA

DNA TRANSFER, ARTIFICIALLY INDUCED

SEE GENETIC MANIPULATION

DOCUMENTATION SYSTEMS

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

DOPA

SEE CYCLIC AMINO ACIDS, DOPA

DOPAMINERGIC RECEPTORS

SEE NEUROTRANSMITTERS RECEPTORS, ADRENERGIC RECEPTORS, DOPAMINERGIC RECEPTORS

DORMANT VIRUS DISEASES

SEE VIRUS DISEASE CHARACTERISTICS, LATENT DORMANT OR SLOW

DORSAL COLUMN STIMULATOR (ELECTROANALGESIA)

SEE SENSORY DEPRESSION, ANALGESIA BY MASKING, ELECTROANALGESIA

DOSAGE

SEE DOSAGE AND ROUTE, DOSAGE

DOSAGE AND ROUTE, DOSAGE

SEE ALSO DRUGS, PHARMACOLOGY, BIOAVAILABILITY

SEE ALSO RADIATION DOSAGE AND DOSIMETRY

** P01DE-01850-18 0089 Nutritional sources and metabolic roles of fluoride - Effect of skeletal fluoride load on retention of administered fluoride

P50DE-02668-15 0212 Regional dental research center - Determination of risk related to alcohol consumption before pregnancy recognition

R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

DOSAGE AND ROUTE, RATE AND DURATION OF ADMINISTRATION

SEE ALSO DRUGS, SLOW RELEASE PREPARATIONS

R23DE-05155-02 Active principles of dental pulp therapeutic agents

R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

R01DE-06000-01 Effect of parotid function on saliva and cells

DOSAGE AND ROUTE, TOPICAL APPLICATION

SEE ALSO DRUGS, PHARMACOLOGY, BIOAVAILABILITY

SEE ALSO GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT, DRUGS

R23DE-05155-02 Active principles of dental pulp therapeutic agents

R23DE-05240-03 Immunological studies-Caries and periodontal disease (mice)

DOSAGE AND ROUTE, TOPICAL APPLICATION

** P50DE-02731-15 0038 Development support for dental research institute - Antiviral chemotherapy--Drug delivery component

R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)

R23DE-05572-02 NEW antiviral therapy for oral and other herpes (mice, guinea pig, rabbits)

** R01DE-05596-02 Topically-applied polymers for caries prevention

DOSAGE SCHEDULE

SEE DOSAGE AND ROUTE, DOSAGE

DOSIMETRY, RADIATION

SEE RADIATION DOSAGE AND DOSIMETRY

DOWN'S SYNDROME

SEE GENETIC DISORDERS, DOWN'S SYNDROME

DOXORUBICIN

SEE ANTIBIOTICS, ANTHRACYCLINES, ADRIAMYCIN

DRINKING BEHAVIOR (ALCOHOL)

SEE ALCOHOLISM - DRINKING, ALCOHOL CONSUMPTION

DRINKING WATER

SEE WATER SUPPLY

DRIVE

SEE PSYCHOLOGY, MOTIVATION

DROPSY

SEE BODY FLUID BALANCE, EDEMA

DRUG BIOAVAILABILITY

SEE DRUGS, PHARMACOLOGY, BIOAVAILABILITY

DRUG DESIGN

SEE DRUGS SYNTHESIS, DESIGN AND PRODUCTION

DRUG INDUCED CONGENITAL ABNORMALITIES

SEE CONGENITAL ABNORMALITIES, DRUG INDUCED

DRUG-INDUCED DIABETES

SEE CARBOHYDRATES METABOLISM DISORDERS, DIABETES, DRUG-INDUCED

DRUG INTERACTIONS WITH NUTRIENTS

SEE NUTRIENTS AND PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION

DRUG METABOLISM

SEE DRUGS, PHARMACOLOGY, BIOCHEMICAL

DRUGS, BLOOD (PLASMA) LEVEL

SEE DRUGS, PHARMACOLOGY, BIOAVAILABILITY

DRUGS, CHEMOTHERAPY

SEE ALSO CONNECTIVE TISSUE DISORDERS CHEMOTHERAPY

SEE ALSO DENTAL DISORDERS CHEMOTHERAPY

SEE ALSO DOSAGE AND ROUTE, RATE AND DURATION OF ADMINISTRATION

SEE ALSO DRUGS, PHARMACOLOGY

SEE ALSO DRUGS, PHARMACOLOGY, BIOAVAILABILITY

SEE ALSO NEOPLASTIC THERAPY, CANCER CHEMOTHERAPY

R01DE-05218-03 DNA homologies among bacteria of periodontal diseases

DRUGS, CHEMOTHERAPY, DRUGS

COMBINATION

SEE ALSO NEOPLASTIC THERAPY, COMBINATION

ANTINEOPLASTIC THERAPY

R01DE-03666-07 X-ray therapeutic index for salivary glands

R01DE-04835-03 Anti-caries mechanism of fluoride complexes

in vitro (human)

N01DE-72409-08 Effect of strontium, lithium and fluorine on dental plaque (rats, human)

DRUGS, GASTROINTESTINAL ABSORPTION

SEE GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT, DRUGS

DRUGS, PHARMACOLOGY

SEE ALSO CHEMICAL STRUCTURE-BIOLOGICAL ACTIVITY

SEE ALSO DENTAL PHARMACOLOGY

SEE ALSO DRUGS, CHEMOTHERAPY

SEE ALSO DRUGS AND PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION

SEE ALSO GENETICS, PHARMACOGENETICS*

SEE ALSO NEUROPHARMACOLOGY

SEE ALSO PHARMACOLOGY STUDY SECTION

SEE ALSO PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION (BIOLOGICAL AND ECOLOGICAL)

SEE ALSO PREGNANCY, EMBRYO-FETUS PHARMACOLOGY

** R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

DRUGS, PHARMACOLOGY, BIOAVAILABILITY

SEE ALSO DOSAGE AND ROUTE, RATE AND DURATION OF ADMINISTRATION

SEE ALSO GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT, DRUGS

P50DE-02731-15 0038 Development support for dental research institute - Antiviral chemotherapy--Drug delivery component

R01DE-05334-02 Periodontal therapy by controlled local drug delivery (human)

R01DE-06113-01 Determinants of fluoride in the oral environment (Dogs, rats)

DRUGS, PHARMACOLOGY, BIOCHEMICAL

SEE ALSO CHEMICAL STRUCTURE-BIOLOGICAL ACTIVITY

SEE ALSO DRUGS RECEPTORS

R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine

R01DE-05089-03 Oral herpes simplex--An approach to dental therapy (hamsters)

R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

** R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)

R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)

DRUGS, PHARMACOLOGY, STIMULATION, CHEMICAL

** R23DE-05072-03 Stimulation of regenerating rat submandibular glands

DRUGS, SLOW RELEASE PREPARATIONS

SEE ALSO DRUGS, PHARMACOLOGY, BIOAVAILABILITY

P50DE-02731-15 0038 Development support for dental research institute - Antiviral chemotherapy--Drug delivery component

DRUGS ADDICTION ANTAGONISTS

R01DE-05204-03 Operant neural control in trigeminal pain systems (rat)

DRUGS ADVERSE EFFECTS

SEE ALSO CONGENITAL ABNORMALITIES, DRUG INDUCED

SEE ALSO DISEASES, COMPLICATIONS, ANESTHESIA RELATED

SEE ALSO DOSAGE AND ROUTE, RATE AND DURATION OF ADMINISTRATION

SEE ALSO DRUGS, PHARMACOLOGY, BIOAVAILABILITY

SEE ALSO PREGNANCY, EMBRYO-FETUS DRUGS ADVERSE EFFECTS

P50DE-02668-15 0172 Regional dental research center -

Genetic and environmental factors interaction in development of cleft lip (mice)

R01DE-04622-05 Craniofacial anomalies and protein receptors

(mice, human)

R01DE-05334-02 Periodontal therapy by controlled local drug

delivery (human)

R01DE-05440-02 H-2 and teratogen-induced craniofacial

malformation (mice)

** R01DE-05459-02 Phenytoin--Pathogenesis of gingival

overgrowth (cats)

** R23DE-05507-02 Psychomotor impairment related to N2O

exposure (human)

R01DE-05525-02 Nature of the permeability barrier in oral

epithelium

R01DE-05678-02 Salivary changes after cancer

chemotherapeutic drugs

DRUGS ADVERSE EFFECTS EMBRYO-FETAL

SEE PREGNANCY, EMBRYO-FETUS DRUGS ADVERSE EFFECTS

DRUGS AND PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION

SEE ALSO DRUGS INTERACTION

SEE ALSO NEOPLASTIC THERAPY, COMBINATION

ANTINEOPLASTIC THERAPY

N01DE-02427-04 Synthesize noncariogenic sweeteners

R01DE-04235-06 Peroxidase in saliva and prevention of oral

disease (human, S mutants)

R01DE-04615-04 Fluoride-cadmium interaction in dental caries

(rats, human)

R01DE-04616-04 Fluoride-cadmium interaction in dental caries

(rats)

R01DE-04957-03 Bacterial metabolites in oral diseases

DRUGS COMBINATION

SEE DRUGS, CHEMOTHERAPY, DRUGS COMBINATION

DRUGS INTERACTION

SEE ALSO DRUGS, CHEMOTHERAPY, DRUGS COMBINATION

SEE ALSO DRUGS AND PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION

** P01DE-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)

R01DE-03856-07 Fluoride-selenium interaction in dental caries (rats)

R23DE-05809-01 Effects of fluoride on physiology of oral bacteria

DRUGS RECEPTORS

SEE ALSO ENDOCRINOLOGY, HORMONE RECEPTORS

SEE ALSO NEUROTRANSMITTERS RECEPTORS, ENDORPHIN RECEPTORS

** R01DE-04622-05 Craniofacial anomalies and protein receptors

(mice, human)

R01DE-05041-03 Orofacial anomalies in phenytoin

teratogenesis (mice, human)

DRUGS RESISTANCE, MICROBIAL

SEE ALSO GENETICS, MICROBIAL

P01DE-02847-13 0022 Microbial ecology and its relation to dental disease - Cemental caries as a dental problem (human, rats, primates)

R01DE-03487-10 Inhibition of human cariogenic streptococci

P50DE-04898-05 0003 Periodontal disease research center -

Therapy and prevention of periodontal diseases (human)

** R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)

** R01DE-06070-01 Antibiotic susceptibilities of periodontal bacteria

N01DE-72409-08 Effect of strontium, lithium and fluorine on

dental plaque (rats, human)

DRUGS SCREENING

R01DE-04439-04 Dental calculus formation using calcifiable

lipoprotein analogues

R01DE-05102-04 Potential anti-caries agents (rats)

** R01DE-72409-08 Effect of strontium, lithium and fluorine on dental plaque (rats, human)

DRUGS SYNTHESIS, DESIGN AND PRODUCTION

** N01DE-02427-04 Synthesize noncariogenic sweeteners

** R01DE-02428-04 Synthesis of noncariogenic sweeteners

(mice)

R01DE-04439-04 Dental calculus formation using calcifiable

lipoprotein analogues

** R01DE-04744-04 New antimicrobial agents for preventing oral diseases

R01DE-05089-03 Oral herpes simplex--An approach to dental

therapy (hamsters)

** R01DE-05476-02 Novel peptide derived sweeteners

Topically-applied polymers for caries

prevention

N01DE-72408-06 Cross-reacting antigens/oral flora acidogenic

bacteria

DRUGS TOXICOLOGY

SEE DRUGS ADVERSE EFFECTS

DRUGS VEHICLES

SEE ALSO DRUGS, PHARMACOLOGY, BIOAVAILABILITY

** R01DE-05334-02 Periodontal therapy by controlled local drug delivery (human)

DSR

SEE RADIOGRAPHY, SCANNING, DSR

D-TYPE VIRUSES

SEE VIRUSES, RETROVIRIDAE

DUODENUM

SEE GASTROINTESTINAL SYSTEM, INTESTINES, SMALL INTESTINE, DUODENUM

DURATION OF TREATMENT

SEE DOSAGE AND ROUTE, RATE AND DURATION OF ADMINISTRATION

DYES, FLUORESCENT DYES AND PROBES

SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOFLOURESCENCE*

R01DE-03739-09 Glycosyltransferases from oral bacteria (bacteria)

DYNAMIC SPATIAL RECONSTRUCTOR

SEE RADIOGRAPHY, SCANNING, DSR

DYSKINESIA AND ATAXIA (CEREBELLAR)

SEE CONGENITAL ABNORMALITIES, BRAIN, CEREBELLOMEDULLARY DYSPLASIA

DYSPLASIA

SEE CONGENITAL ABNORMALITIES, BRAIN, CEREBELLOMEDULLARY DYSPLASIA

EAR

R23DE-05393-03 Factors association with hyperplasia of oral mucosa

EAR, LABYRINTH, VESTIBULAR APPARATUS

P01DE-02848-11 0002 Biology of connective tissue, bones, and teeth - Steroid receptors in craniofacial teratology (mice)

EAR, MIDDLE EAR, EUSTACHIAN TUBE

P01DE-01697-19 0035 A research program in craniofacial problems - Non-human primate model of cleft palate (monkeys)

** P01DE-01697-19 0041 A research program in craniofacial problems -

EAR DISORDERS, HEARING DISORDERS

P01DE-01697-19 0039 A research program in craniofacial problems - Otitis media and its consequences (human)

P01DE-01697-19 0041 A research program in craniofacial problems -

R01DE-04517-03 Pin-retained prosthesis with surgery in cleft

palate

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

EAR DISORDERS, MIDDLE EAR DISORDERS

- ** P01DE-01697-19 0035 A research program in craniofacial problems - Non-human primate model of cleft palate (monkeys)
R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate

EAR DISORDERS, MIDDLE EAR DISORDERS, OTITIS MEDIA

- ** P01DE-01697-19 0039 A research program in craniofacial problems - Otitis media and its consequences (human)

EAR DISORDERS CONGENITAL

SEE CONGENITAL ABNORMALITIES, EAR (GENERAL)

EAR DISORDERS DIAGNOSIS, HEARING TESTS*

- P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

EAR SURGERY, MYRINGOPLASTY

- P01DE-01697-19 0039 A research program in craniofacial problems - Otitis media and its consequences (human)

EAR SURGERY, TYMPANOPLASTY

- SEE ALSO EAR SURGERY, MYRINGOPLASTY
P01DE-01697-19 0039 A research program in craniofacial problems - Otitis media and its consequences (human)

EARLY CHILDHOOD

SEE CHILDREN, PRESCHOOL (1 TO 6 YRS)

EARLY DIAGNOSIS

SEE DIAGNOSTIC TESTS, EARLY DIAGNOSIS*

EARLY EMBRYONIC STAGES

SEE EMBRYOLOGY, EARLY EMBRYONIC STAGES (1-28 DAYS)

ECOLOGICAL TOXICOLOGY

SEE TOXICOLOGY, ENVIRONMENTAL

ECOLOGY MICROORGANISMS

SEE ENVIRONMENT, ECOLOGY ORGANISMS

ECONOMICS

SEE SOCIOECONOMICS

EDEMA

SEE BODY FLUID BALANCE, EOEMA

EDENTULOUS MOUTH

SEE DENTAL DISORDERS, TOOTH LOSS

EDETIC ACID

SEE AMINO ACIDS, ETHYLENEDIAMINO ACIDS, EDTA

EDTA

SEE AMINO ACIDS, ETHYLENEDIAMINO ACIDS, EDTA

EDUCATION, HEALTH EDUCATION

SEE ALSO PSYCHOLOGY, ATTITUDE TO HEALTH AND HEALTH PROBLEMS

- R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)

EDUCATION, HEALTH EDUCATION, DENTAL

- ** R01DE-05511-02 Evanston-Oak park fluoridation study after 25 years (human)

EDUCATION, HEALTH OCCUPATIONS, DENTAL

R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)

- ** R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)

EDUCATION, SCHOOLS

R01DE-05371-01 Psychosocial evaluation of craniofacial patients

- ** N01DE-92421-14 National caries prevalence survey

EDUCATION, TRAINING

SEE ALSO INFORMATION DISSEMINATION, MEETINGS CONFERENCES SYMPOSIA, WORKSHOP

- ** R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)

EGF

SEE GROWTH FACTORS (INCL. ANABOLICS), EPIDERMAL GROWTH FACTOR

EHLERS-DANLOS SYNDROME

SEE METABOLIC DISORDERS (NBORN, EHLERS-DANLOS SYNDROME)

8,11,14-EICOSATRIENOATE, HYDROGEN-

DONOR: OXYGEN OXIDOREDUCTASE
SEE OXIDOREDUCTASES, PROSTAGLANDIN SYNTHASE

ELASTASE

SEE PROTEASES AND PEPTIDASES, ELASTASE

ELASTIC TISSUE

SEE CONNECTIVE TISSUE, ELASTIC TISSUE

ELASTICITY

SEE PHYSICAL PROPERTIES, ELASTICITY

ELASTIN

SEE ALBUMINOIDS, ELASTIN

ELASTOGRAPHY

SEE PHYSICAL PROPERTIES, ELASTICITY

ELASTOMERS

SEE PLASTICS, ELASTOMERS

ELECTRICAL FIELDS

SEE ELECTRICITY-MAGNETISM, ELECTRICAL FIELDS

ELECTRICAL MASKING OF PAIN

SEE SENSORY DEPRESSION, ANALGESIA BY MASKING, ELECTROANALGESIA

ELECTRICAL POTENTIALS

SEE ELECTROPOTENTIALS

ELECTRICITY-MAGNETISM, ELECTRICAL FIELDS

R23DE-05945-01 Physicochemical modifications of dental restoratives

ELECTROANALGESIA

SEE SENSORY DEPRESSION, ANALGESIA BY MASKING, ELECTROANALGESIA

ELECTROANESTHESIA

SEE SENSORY DEPRESSION, ANALGESIA BY MASKING, ELECTROANALGESIA

ELECTROCHEMISTRY

SEE CHEMISTRY, ELECTROCHEMISTRY

ELECTRODIFFUSION

SEE BIOLOGICAL TRANSPORT, PASSIVE TRANSPORT, DIFFUSION

ELECTROENCEPHALOGRAPHY

SEE BRAIN ELECTRICAL ACTIVITY

ELECTROGENIC ION PUMP

SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS

ELECTROLYTE EXCHANGE AND TRANSPORT

SEE BIOLOGICAL TRANSPORT, ION EXCHANGE AND TRANSPORT

ELECTROLYTES

SEE IONS, ELECTROLYTES

ELECTROMYOGRAPHY

SEE MUSCLE FUNCTION, ELECTROMYOGRAPHY*

ELECTRON MICROSCOPY

SEE OPTICS, MICROSCOPY, ELECTRON*

ELECTROPHYSIOLOGY

SEE ALSO BRAIN ELECTRICAL ACTIVITY

SEE ALSO ELECTROPOTENTIALS

SEE ALSO ELECTROSTIMULUS

SEE ALSO NEUROPHYSIOLOGY (GENERAL)

- P50DE-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli

- ** P50DE-02668-15 0209 Regional dental research center - Static and dynamic properties of S-I neurons in the behaving macaque monkey

R01DE-05271-03 Neuroeffector transmission in a simple

salivary gland (snails, mice)

R01DE-05390-03 Opiate action on CNS terminals of tooth pulp

fibers (animals)

R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis

(cats)

ELECTROPOTENTIALS

- P50DE-02668-15 0209 Regional dental research center - Static and dynamic properties of S-I neurons in the behaving macaque monkey

R23DE-05945-01 Physicochemical modifications of dental restoratives

ELECTROPOTENTIALS, ACTION POTENTIALS

R01DE-04610-03 Physiological studies on mastication

(human)

R01DE-05271-03 Neuroeffector transmission in a simple

salivary gland (snails, mice)

ELECTROPOTENTIALS, EVOKED POTENTIALS

- P50DE-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli

P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

- ** P01DE-05130-03 0009 Dental/orofacial pain--Mechanisms behavior and modulation - Dental near and far field potentials and pain reactivity (cats, monkeys)

R01DE-05204-03 Operant neural control in trigeminal pain

systems (rat)

R01DE-05390-03 Opiate action on CNS terminals of tooth pulp

fibers (animals)

R01DE-05679-01 Pathophysiology of MPD and other facial

pain syndromes (animals)

ELECTROPOTENTIALS, MEMBRANE POTENTIALS

R01DE-04385-06 Mechanism of dental caries (human)

- ** R01DE-04487-05 Pulsating forces in orthodontics (human)

R01DE-05271-03 Neuroeffector transmission in a simple

salivary gland (snails, mice)

R01DE-05354-04 Prevention of dental caries (rats, human)

ELECTROSTIMULUS

R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)

R01DE-04004-07 Acupuncture and perception of dental pain

(human)

- ** R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)

P01DE-05130-03 0006 Dental/orofacial pain--Mechanisms behavior and modulation - Acute pain in research and clinical settings

- ** R01DE-05412-02 Electric current, bone remodeling and tooth movement (cats)

ELECTROVALENT BONDS

SEE CHEMICAL BONDS, IONIC

ELEMENTS, TRACE

SEE CHEMICALS (GENERAL), ELEMENTS, TRACE ELEMENTS

EMBRYO, MAMMALIAN

SEE PREGNANCY, EMBRYO-FETUS

EMBRYO CELLS AND TISSUES

SEE EMBRYOLOGY, EMBRYO-FETAL CELLS AND TISSUES

EMBRYO CULTURE

SEE PREGNANCY, EMBRYO-FETUS CULTURE

EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS

SEE PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)

EMBRYO-FETUS DRUGS ADVERSE EFFECT

SEE PREGNANCY, EMBRYO-FETUS DRUGS ADVERSE EFFECTS

EMBRYO-FETUS PHARMACOLOGY

SEE PREGNANCY, EMBRYO-FETUS PHARMACOLOGY

EMBRYO-FETUS TOXICOLOGY

SEE PREGNANCY, EMBRYO-FETUS TOXICOLOGY

EMBRYOLOGY

SEE ALSO GENETICS, DEVELOPMENTAL GENETICS

R01DE-03715-06 Cellular assembly--Its role in facial

morphogenesis (fungi)

R01DE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)

- ** R01DE-05138-03 Visceral arches and oro-facial morphogenesis (mice, monkeys)

EMBRYOLOGY, EARLY EMBRYONIC STAGES (1-28 DAYS)

R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

R01DE-05550-01 Cell death during craniofacial embryogenesis

- ** R01DE-05555-01 Cell migration in the teleost embryo

** R01DE-05630-01 Matrix/cell surface in neural crest cell

morphogenesis (mice, chick, quail)

R01DE-05669-01 Chorion type and dental morphology in twins

EMBRYOLOGY, EMBRYO-FETAL CELLS AND TISSUES

SEE ALSO PREGNANCY, EMBRYO-FETUS

SEE ALSO TISSUE (CELL) CULTURE, EMBRYONIC-FETAL CELL LINES

R01DE-02103-17 Inductive substrates of tooth and bone

(rats, cattle, mice, rabbits, human)

EMBRYOLOGY, GERM LAYERS

SEE ALSO CONNECTIVE TISSUE, MESENCHYME

- ** R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)

- ** R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

EMBRYOLOGY (HUMAN) AND DEVELOPMENT STUDY SECTION

- ** R01DE-03469-10 Teratogens effects on cleft palate formation (mice)

- ** R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)

- ** R01DE-04731-05 Analysis of primary palate formation (chick embryo)

- ** R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)

- ** R01DE-05041-03 Orofacial anomalies in phenytoin teratogenesis (mice, human)

- ** R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

- ** R01DE-05168-03 Glucocorticoid receptors and cleft palate (mice)

- ** R01DE-05367-02 Cranio-facial anomalies in the oel mouse

- ** R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)

** R01DE-05550-01 Cell death during craniofacial embryogenesis

** R01DE-05555-01 Cell migration in the teleost embryo

- ** R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)

EMBRYONIC CELL LINES

SEE TISSUE (CELL) CULTURE, EMBRYONIC-FETAL CELL LINES

EMOTIONAL ADJUSTMENT

SEE PSYCHOLOGICAL ADAPTATION, EMOTIONAL ADJUSTMENT

EMOTIONAL STRESS

SEE PSYCHOLOGIC STRESS

ENAMEL

SEE DENTAL STRUCTURE, ENAMEL

ENAMEL ORGAN

SEE DENTAL STRUCTURE, ENAMEL ORGAN

ENCEPHALITIS

SEE NERVOUS DISORDERS CENTRAL, ENCEPHALITIS

ENCEPHALOGRAPHY

SEE BRAIN VISUALIZATION, ENCEPHALOGRAPHY*

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

ENDOCARDITIS BACTERIAL

SEE HEART DISORDERS, ENDOCARDITIS BACTERIAL

ENDOCRINE GLANDS

SEE ENDOCRINOLOGY, ENDOCRINES

ENDOCRINE REGULATION AND CONTROL (MECHANISMS)

SEE ENDOCRINOLOGY, HORMONAL REGULATION AND CONTROL (MECHANISMS)

ENDOCRINOLOGY, ENDOCRINES

SEE ALSO BLOOD AND RE SYSTEM, THYMUS

SEE ALSO TISSUE, EXOCRINE GLANDS (GENERAL)

R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

ENDOCRINOLOGY, ENDOCRINE SURGERY

SEE PARATHYROIDECTOMY

ENDOCRINOLOGY, HORMONAL REGULATION AND CONTROL (MECHANISMS)

P01DE-01850-18 0068 Nutritional sources and metabolic roles of fluoride - Radioimmunoassay of parathyroid hormone in the rat

P50DE-02668-15 0192 Regional dental research center - Skeletal actions of calcitonin in the rat

P50DE-02668-15 0213 Regional dental research center - Hormone action is the salivary glands of inbred mice

** R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)

R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)

R23DE-05142-03 Control mechanisms in salivary gland development (rats)

R01DE-05255-03 Regulation of collagenase and bone resorption (chick embryos, mice)

R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

** R23DE-05491-02 Control of biomineralization in two species (snails)

R01DE-05632-01 Development of salivary gland secretory function (rats)

R23DE-05985-01 Growth factors in salivary secretions

ENDOCRINOLOGY, HORMONE BINDING**PROTEINS**

R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

ENDOCRINOLOGY, HORMONE RECEPTORS

** P01DE-02848-11 0002 Biology of connective tissue, bones, and teeth - Steroid receptors in craniofacial teratology (mice)

R01DE-04039-04 Sex steroid metabolism in oral tissues

R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

** R01DE-05168-03 Glucocorticoid receptors and cleft palate (mice)

R01DE-05322-01 Genetic analysis of birth defects involving septa (human, mice)

R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

ENDOCRINOLOGY, HORMONES, STEROID**HORMONES**

SEE ALSO ADRENAL CORTIX HORMONES

SEE ALSO ANDROSTANE SERIES, ANDROGENS

SEE ALSO ESTRADIENE SERIES, ESTROGENS

SEE ALSO PROGESTINS

SEE ALSO REPRODUCTIVE HORMONES, SEX HORMONES

** P01DE-02848-11 0002 Biology of connective tissue, bones, and teeth - Steroid receptors in craniofacial teratology (mice)

** R01DE-04039-04 Sex steroid metabolism in oral tissues

ENDOCRINOLOGY, HORMONES BIOSYNTHESIS

SEE ALSO PROTEINS BIOSYNTHESIS

R01DE-04844-04 Stress-related bone resorption--Mechanisms of action (rats)

ENDOCRINOLOGY, HORMONES METABOLISM, STEROID HORMONES METABOLISM

** R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

R01DE-05168-03 Glucocorticoid receptors and cleft palate (mice)

ENDOCYTOSIS

SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, PINOCYTOSIS

ENDOD

SEE PLANTS, ANGIOSPERMS, POKEWEED*

ENDODONTICS

SEE DENTISTRY, ENDODONTICS

ENDOPEROXIDES

SEE FATTY ACIDS, UNSATURATED, PROSTAGLANDINS

ENDOPASMIC RETICULUM

SEE CELL COMPONENTS, ENDOPLASMIC RETICULUM

ENDORPHIN RECEPTORS

SEE NEUROTRANSMITTERS RECEPTORS, ENDORPHIN RECEPTORS

ENDORPHINS

SEE PITUITARY-DIENCEPHALON HORMONES, ENDORPHINS

ALPHA-ENDORPHIN

SEE PITUITARY-DIENCEPHALON HORMONES, ENDORPHINS

BETA-ENDORPHIN

SEE PITUITARY-DIENCEPHALON HORMONES, ENDORPHINS

ENDOSSEOUS ARTIFICIAL TOOTH IMPLANT

SEE DENTAL PROSTHESIS, DENTAL IMPLANT ENDOSSEOUS

ENDOTHELIUM VASCULAR PERMEABILITY

SEE CARDIOVASCULAR SYSTEM, ENDOTHELIUM PERMEABILITY

ENDOTOXINS

SEE IMMUNOLOGY, ANTIGENS BACTERIAL, ENDOTOXINS

ENDOXAN

SEE HALDALKYLAMINES, CYCLOPHOSPHAMIDE

ENERGY DEPENDENT TRANSPORT

SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT

ENGINEERING, BIOMEDICAL

SEE BIOMEDICAL ENGINEERING

ENGINEERING, HUMAN

SEE INJURY (HAZARDS) PREVENTION AND CONTROL, SAFETY EQUIPMENT-ENGINEERING

ENKEPHALIN

SEE PEPTIDES, ENKEPHALIN

ENKEPHALIN RECEPTORS

SEE NEUROTRANSMITTERS RECEPTORS, ENDORPHIN RECEPTORS

ENTERIC FEEDING

SEE NUTRITION, DIET SCHEDULE AND ROUTE, TUBE FEEDING

ENVIRONMENT, ALTITUDE

R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

ENVIRONMENT, ECOLOGY ORGANISMS

SEE ALSO POPULATION STUDIES MICROORGANISMS

R01DE-03180-11 Microbiologic studies of the human oral streptococci

** R01DE-05180-03 Composition of S mutants in different growth environments

ENVIRONMENT, ECOLOGY ORGANISMS, HOST-ORGANISM

SEE ALSO VIRUS DISEASE CHARACTERISTICS, HOST-VIRUS

R01DE-01554-20 Host factors in caries resistance (human, rats)

M P01DE-02847-13 Microbial ecology and its relation to dental disease

R01DE-04296-07 Lysozyme--Cell surface interactions and oral defense

P50DE-04881-05 0003 Center for clinical research in periodontal diseases - Host immunologic response to oral microorganisms

R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)

** R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)

** R13DE-05753-01 Symposium on host-bacteria in periodontal diseases

ENVIRONMENT, ORIENTATION, CHEMOTAXIS

P50DE-02600-15 0030 Support for oral biology research center - Leukocyte function--Its role in periodontal disease (human)

R01DE-03469-10 Teratogens effects on cleft palate formation (mice)

R01DE-03715-06 Cellular assembly--Its role in facial morphogenesis (fungi)

R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)

R01DE-04844-04 Stress-related bone resorption--Mechanisms of action (rats)

P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)

P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)

R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

ENVIRONMENT, STRESS

SEE ALSO PSYCHOLOGIC STRESS

R01DE-04990-03 Normal and abnormal faces (human)

ENVIRONMENT, STRESS MECHANICAL

SEE ALSO DENTAL STRESS ANALYSIS

SEE ALSO PHYSICAL PROPERTIES, TENSILE STRENGTH

SEE ALSO SKELETAL STRESS

P50DE-02600-15 0028 Support for oral biology research center - Repletion and coupling in bone volume regulation (rat)

R01DE-02936-13 Marginal fracture of dental amalgam

R01DE-03545-09 Prediction of tooth displacement (human)

R01DE-04252-07 Semi and nonprecious metal-porcelain systems

R01DE-04394-05 Pin and slot retention in amalgam and composite materials

R01DE-04487-05 Pulsating forces in orthodontics (human)

R01DE-04531-04 Strain in the facial bones of (primates)

R01DE-05637-01 Mechanical properties of dental composite materials

ENVIRONMENT CONTROLLED

R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

ENVIRONMENTAL HEALTH (GENERAL)

SEE ALSO EPIDEMIOLOGY AND DISEASE CONTROL STUDY SECTION

** P50DE-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)

ENVIRONMENTAL TOXICOLOGY

SEE TOXICOLOGY, ENVIRONMENTAL

ENZYME DEFICIENCY DISORDERS

SEE METABOLIC DISORDERS INBORN

ENZYME DEREPRESSION

SEE ENZYME INDUCTION-REPRESSION-DEREPRESSION

ENZYME INDUCTION

SEE ENZYME INDUCTION-REPRESSION-DEREPRESSION

ENZYME INDUCTION-REPRESSION-DEREPRESSION

** R01DE-03715-06 Cellular assembly--Its role in facial morphogenesis (fungi)

R01DE-04039-04 Sex steroid metabolism in oral tissues

R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)

** R01DE-05255-03 Regulation of collagenase and bone resorption (chick embryos, mice)

R01DE-05550-01 Cell death during craniofacial embryogenesis

ENZYME INHIBITORS

SEE ALSO BLOOD COAGULATION, ANTITHROMBINS

SEE ALSO ENZYME SUBSTRATE ANALOGS

** R01DE-03118-11 Inhibition of saccharide metabolism by oral flora

R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)

** R01DE-05102-04 Potential anti-caries agents (rats)

R01DE-05255-03 Regulation of collagenase and bone resorption (chick embryos, mice)

ENZYME INHIBITORS, PHOSPHODIESTERASE INHIBITORS

R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)

ENZYME MECHANISMS

P50DE-02600-15 0032 Support for oral biology research center - Keratohyalin in keratinization of oral mucosa and skin (human, rats)

R01DE-03118-11 Inhibition of saccharide metabolism by oral flora

R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)

R01DE-03578-10 Biosynthetic study of dental plaque polysaccharides

R01DE-03715-06 Cellular assembly--Its role in facial morphogenesis (fungi)

R01DE-03731-06 Dextran sucrose of Streptococcus sanguis

R01DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)

R01DE-04224-07 Genetics of oral microflora

R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)

R01DE-04657-05 Abnormal palatal development induced by haddacidin (fungi)

R01DE-04844-04 Stress-related bone resorption--Mechanisms of action (rats)

R01DE-04957-03 Bacterial metabolites in oral diseases

R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)

R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)

R01DE-05249-02 Salivary secretion-role of calcium (mice)

ENZYME MODELS

R01DE-03715-06 Cellular assembly--Its role in facial morphogenesis (fungi)

ENZYME REPRESSION

SEE ENZYME INDUCTION-REPRESSION-DEREPRESSION

ENZYME STRUCTURE

P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)

R01DE-03715-06 Cellular assembly--Its role in facial morphogenesis (fungi)

R01DE-03731-06 Dextran sucrose of Streptococcus sanguis

R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)

ENZYME SUBSTRATE

R01DE-03118-11 Inhibition of saccharide metabolism by oral flora

R01DE-03715-06 Cellular assembly--Its role in facial morphogenesis (fungi)

R01DE-04278-06 Human saliva-streptococcal metabolic interactions

ENZYME SUBSTRATE ANALOGS

R01DE-03118-11 Inhibition of saccharide metabolism by oral flora

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See Appendix for investigator's name and Grant Number.

(contd.)

ENZYMES

- SEE ALSO CARBOHYDRASES
 SEE ALSO CHEMICAL REACTIONS, CATALYSTS
 SEE ALSO ENZYME INHIBITORS
 SEE ALSO HYDROLASES
 SEE ALSO OXIDOREDUCTASES
 SEE ALSO PEROXIDASES
 SEE ALSO PHOSPHATASES
 SEE ALSO PROTEASES AND PEPTIDASES
 SEE ALSO TRANSFERASES
 R01DE-01554-20 Host factors in caries resistance (human, rats)
 ** P50DE-02668-15 0196 Regional dental research center - Cytiochemical demonstration of macromolecules of craniofacial tissue

ENZYMES, ISOENZYMES

- R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)

EPIDEMIOLOGY, EPIDEMIOLOGIC METHODS

- SEE POPULATION STUDIES HUMAN, EPIDEMIOLOGY

EPIDEMIOLOGY AND DISEASE CONTROL**STUDY SECTION**

- ** R01DE-04068-07 Statistical methods in dental research
 ** R01DE-04358-06 Treatment of temporomandibular joint pain
 ** R01DE-04494-05 Control of stress during dental procedures (human)
 ** R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)
 ** R01DE-05371-01 Psychosocial evaluation of craniofacial patients
 ** R23DE-05497-02 Dental disease and work loss (human)
 ** R01DE-05511-02 Evanston-Oak park fluoridation study after 25 years (human)
 ** R23DE-05527-02 Behavioral treatments for nocturnal bruxism (human)

EPIDERMAL GROWTH FACTOR

- SEE GROWTH FACTORS (INCL. ANABOLICS), EPIDERMAL GROWTH FACTOR

EPIDERMIS

- SEE SKIN (GENERAL)

EPIDERMOID CARCINOMA

- SEE NEOPLASMS, CARCINOMA EPIDERMOID

EPIGLOTTIS

- SEE RESPIRATORY SYSTEM, LARYNX, EPIGLOTTIS

EPILEPSY

- SEE BRAIN DISORDERS, EPILEPSY

EPINEPHRINE

- SEE PHENYLALKYLAMINES, CATECHOLAMINES, EPINEPHRINE

EPIPHYLLOTOXIN

- SEE NAPHTHALENES, METHYLENEDIOXY-, POPYHYLLIN

EPISOMES

- SEE GENETICS, EXTRACHROMOSOMAL INHERITANCE, PLASMIDS

EPITHELIUM

- SEE TISSUE, EPITHELIUM

EQUILIBRIUM SENSE

- SEE SENSORY-PERCEPTUAL PROCESSES, PROPRICEPTION

EQUIPMENT, LABORATORY

- SEE BIOMEICAL FACILITIES

ERYTHEMA

- SEE SKIN DISORDERS, ERYTHEMA

ERYTHROBLASTOSIS (ERYTHROLEUKOSIS)**VIRUS AVIAN**

- SEE VIRUSES, RETROVIRIDAE, LEUKOSIS-SARCOMA AVIAN, LEUKOSIS VIRUSES AVIAN

ERYTHROCYTES

- SEE BLOOD CELLS, ERYTHROCYTES

ERYTHROMYCIN

- SEE ANTIBIOTICS, MACROLIDE ANTIBIOTICS, ERYTHROMYCIN

ESCHERICHIA COLI

- SEE BACTERIA, ENTEROBACTERIACEAE, ESCHERICHIA COLI*

ESOPHAGEAL MUCOSA

- SEE ORAL-PHARYNGEAL, MUCOSA

ESTRADIENE SERIES, ESTROGENS

- R01DE-04039-04 Sex steroid metabolism in oral tissues

ESTROGENS

- SEE ESTRADIENE SERIES, ESTROGENS

ETHAMIVAN

- SEE PHENYLAMIDES

ETHNIC GROUPS

- SEE SOCIAL GROUPS, ETHNIC

ETHOLOGY (ANIMAL BEHAVIOR)

- SEE PSYCHOLOGY, BEHAVIOR ANIMAL

ETHYLENEDIAMINE TETRAACETIC ACID

- SEE AMINO ACIDS, ETHYLENEDIAMINO ACIDS, EDTA

EUSTACHIAN TUBE

- SEE EAR, MIDDLE EAR, EUSTACHIAN TUBE

EVALUATION AND/OR ANALYSIS

- SEE BIOMATERIALS, BIOMATERIALS EVALUATION
 SEE HEALTH CARE (SERVICES) (RESOURCES) ANALYSIS AND EVALUATION
 SEE INFORMATION GATHERING METHODS EVALUATION-STANDARDS
 SEE THERAPY EVALUATION

EVALUATION OF BIOMATERIALS

- SEE BIOMATERIALS, BIOMATERIALS EVALUATION

EVOKE POTENTIALS

- SEE ELECTROPOTENTIALS, EVOKE POTENTIALS

EXCEPTIONAL (HANDICAPPED) CHILDREN

- SEE CHILDREN, HANDICAPPED CHILDREN

EXCHANGE DIFFUSION

- SEE BIOLOGICAL TRANSPORT, PASSIVE TRANSPORT, DIFFUSION

EXCIPIENTS

- SEE DRUGS VEHICLES

EXCRETION

- SEE BIOLOGICAL TRANSPORT, SECRETORY MECHANISMS, EXCRETION

EXHALATION-INHALATION

- SEE RESPIRATORY FUNCTION, RESPIRATION

EXOCHORDAL GLANDS (GENERAL)

- SEE TISSUE, EXOCHORDAL GLANDS (GENERAL)

EXOCYTOSIS

- SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, PINOCYTOSIS

EXOPHTHALMOS

- SEE EYE DISORDERS, EXOPHTHALMOS

EXOTOXINS

- SEE IMMUNOLOGY, ANTIGENS BACTERIAL, EXOTOXINS

EXPECTANCY

- SEE PSYCHOLOGY, COGNITION, EXPECTANCY

EXPERIMENTAL IMMUNOLOGY STUDY SECTION

- ** R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)
 ** R23DE-05789-01 IgA receptor bearing oral cells in cystic fibrosis (human)

EXPERIMENTAL PSYCHOLOGY STUDY SECTION

- SEE BIO-PSYCHOLOGY STUDY SECTION

EXPERIMENTAL VIROLOGY STUDY SECTION

- ** R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)
 ** R23DE-05572-02 NEW antiviral therapy for oral and other herpes (mice, guinea pig, rabbits)

EXPIRATION-INSPIRATION

- SEE RESPIRATORY FUNCTION, RESPIRATION

EXTRACELLULAR SPACE

- SEE BODY FLUIDS, EXTRACELLULAR SPACE (COMPARTMENT)

EXTRACHROMOSOMAL DNA, GENETICS, INHERITANCE

- SEE GENETICS, EXTRACHROMOSOMAL INHERITANCE

EXTRACORPOREAL RADIOASSAY

- SEE RADIOASSAY (RADIOMETRY)

EXTRANUCLEAR DNA

- SEE GENETICS, EXTRACHROMOSOMAL INHERITANCE

EXTRINSIC SURFACE ACTIVITY OF MEMBRANES

- SEE MEMBRANE SURFACE (BIOLOGICAL) ACTIVITY (GENERAL)

EYE

- ** P01DE-02872-12 0058 Craniofacial dysmorphism - Ophthalmology (human, rabbits)

EYE, VISION

- P01DE-02872-12 0038 Craniofacial dysmorphism - Evaluation of craniofacial surgery

EYE, VISUAL FEEDBACK

- R23DE-05799-01 Behavioral methods for pedodontic management (human)

EYE DISORDERS, EXOPHTHALMOS

- P01DE-02872-12 0063 Craniofacial dysmorphism - Premature craniofacial synostoses (human)

EYE DISORDERS, EYELID DISORDERS

- P01DE-02872-12 0058 Craniofacial dysmorphism - Ophthalmology (human, rabbits)
 R01DE-05367-02 Cranio-facial anomalies in the oel mouse

EYE DISORDERS, VISION DISORDERS

- P01DE-02872-12 0055 Craniofacial dysmorphism - Human genetics

EYE DISORDERS CONGENITAL

- SEE CONGENITAL ABNORMALITIES, EYE (GENERAL)

EYE MOVEMENTS

- P01DE-02872-12 0038 Craniofacial dysmorphism - Evaluation of craniofacial surgery

EYE REFRACTIVE DISORDERS, ASTIGMATISM

- P01DE-02872-12 0058 Craniofacial dysmorphism - Ophthalmology (human, rabbits)

EYE SURGERY

- P01DE-02872-12 0058 Craniofacial dysmorphism - Ophthalmology (human, rabbits)

EYELID DISORDERS

- SEE EYE DISORDERS, EYELID DISORDERS

F

- SEE HALOGENS, FLUORINE (COMPOUNDS) SEE ALSO SPECIFICS

F1 HYBRID DISEASE (TRANSPLANTATION)

- SEE TISSUE COMPATIBILITY-TRANSPLANT, GRAFT VERSUS HOST REACTIONS

FACE

- SEE BODY REGIONS, HEAD, FACE

FACE NEOPLASMS

- SEE NEOPLASMS OF BODY REGIONS, HEAD AND NECK

FACIAL ANOMALIES

- SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL

FACIAL EXPRESSION

- SEE INFORMATION-COMMUNICATION BEHAVIOR, FACIAL EXPRESSION

FACIAL MUSCLES

- SEE MUSCLES, FACIAL MUSCLES

FACIAL PAIN

- SEE ORAL-FACIAL PAIN

FACIAL PARALYSIS

- SEE NERVOUS DISORDERS PERIPHERAL, FACIAL PARALYSIS

FACIAL RESTORATION

- SEE ORAL-FACIAL RESTORATION

FACILITATED DIFFUSION

- SEE BIOLOGICAL TRANSPORT, PASSIVE TRANSPORT, DIFFUSION

FACILITIES

- SEE BIOMEICAL FACILITIES
 SEE BIOMEDICAL SYSTEMS AUTOMATED

FACTOR II

- SEE BLOOD COAGULATION, PROTHROMBIN

FACTOR X

- SEE BLOOD COAGULATION, FACTOR X

FAILURE TO THRIVE INTRAUTERINE

- SEE PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)

FAILURE TO THRIVE POSTNATAL

- SEE GROWTH DISORDERS POSTNATAL (SEE ALSO APPROPRIATE SPECIFICS)

FAMILIAL DISORDERS

- SEE GENETIC DISORDERS (SEE ALSO APPROPRIATE CONGENITAL ABNORMALITIES)

FAMILIAL DISORDERS, METABOLIC ERRORS

- SEE METABOLIC DISORDERS INBORN

FAMILY

- SEE ALSO CHILDREN
 P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)
 P01DE-02872-12 0061 Craniofacial dysmorphism - Craniofacial dysmorphism
 R01DE-04779-04 Behavioral stages for cleft palate patients
 R01DE-05371-01 Psychosocial evaluation of craniofacial patients

FAMILY, PARENT-OFFSPRING

- R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years

FAMILY, PARENT-OFFSPRING, MOTHER-CHILD INTERACTION

- P01DE-02872-12 0057 Craniofacial dysmorphism - Speech and hearing testing (human)

FAMILY, SIBLING ORDER

- ** R23DE-05942-01 Airway factors in cleft palate dentofacial deformity
 ** R23DE-05951-01 Selective microbial ecology of periodontosis siblings

FAMILY, TWINS AND MULTIPLETS

- R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
 ** R01DE-05669-01 Chorion type and dental morphology in twins

FASTING

- SEE NUTRITION, DIET, FASTING

FAT-SOLUBLE VITAMINS

- SEE VITAMIN A
 SEE VITAMIN D GROUP

FATTY ACIDS, ARACHIDONIC ACID

- R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)

(contd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

FATTY ACIDS, CAPRYLIC ACID

- ** P01DE-01850-18 0075 Nutritional sources and metabolic roles of fluoride - Metabolic handling of perfluorooctanoic acid (rats)

FATTY ACIDS, LACTATES

- SEE ALSO OXIDOREDUCTASES, LACTATE DEHYDROGENASE
R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism

FATTY ACIDS, PALMITIC ACID

- R23DE-05393-03 Factors association with hyperplasia of oral mucosa

FATTY ACIDS, PYRUVATES

- SEE ALSO PHOSPHOTRANSFERASES, ATP-PYRUVATE PHOSPHOTRANSFERASE
R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism

FATTY ACIDS, UNSATURATED,**PROSTAGLANDINS**

- SEE ALSO OXIDOREDUCTASES, PROSTAGLANDIN SYNTHASE
R01DE-02110-17 Salivary gland structure and function (rats)
R01DE-03301-11 Connective tissue of the periodontium—Collagen maturation
** R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)
R01DE-04039-04 Sex steroid metabolism in oral tissues
R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)
R01DE-04844-04 Stress-related bone resorption—Mechanisms of action (rats)
** P50DE-04881-05 0003 Center for clinical research in periodontal diseases - Host immunologic response to oral microorganisms
R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)
R23DE-05332-03 Bone in vitro—Ultrastructure and autoradiography (mice)
R01DE-05412-02 Electric current, bone remodeling and tooth movement (cats)
R01DE-05413-02 Bone resorption in periodontal disease
R01DE-05494-02 Activation of macrophages in periodontal disease
R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)
** R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)
R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

FATTY ACIDS, UNSATURATED, PROSTAGLANDINS ANALOGS

- ** R23DE-05967-01 Role of prostaglandin E in periodontal disease activity

FC RECEPTOR

- SEE IMMUNOLOGY, ANTIBODIES, ANTIBODY RECEPTORS

FE

- SEE IRON

FEAR, DENTAL

- SEE DENTAL FEAR AND ANXIETY

FEEDBACK, SENSOR

- SEE SENSORY FEEDBACK

FEEDBACK, VISUAL

- SEE EYE, VISUAL FEEDBACK

FEEDBACK CONTROL (NEURAL)

- SEE INFORMATION PROCESSING AND CONTROL (NEURAL)

FEEDS, ANIMAL

- SEE FOOD, ANIMAL FEEDS

FEMUR

- SEE SKELETAL SYSTEM, LIMB BONES, FEMUR

FETAL ALCOHOL DISORDERS

- SEE PREGNANCY DISORDERS, EMBRYO-FETAL DISORDERS, FETAL ALCOHOL DISORDERS

FETAL CELL LINES

- SEE TISSUE (CELL) CULTURE, EMBRYONIC-FETAL CELL LINES

FETAL CELLS AND TISSUES

- SEE EMBRYOLOGY, EMBRYO-FETAL CELLS AND TISSUES

FETAL CULTURE

- SEE PREGNANCY, EMBRYO-FETUS CULTURE

FETAL FAILURE TO THRIVE

- SEE PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)

FETAL GROWTH DISORDERS

- SEE PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)

FETAL NUTRITION

- SEE NUTRITION, MATERNAL-FETAL NUTRITION

FETAL TOXICOLOGY

- SEE PREGNANCY, EMBRYO-FETUS TOXICOLOGY

FETUS

- SEE PREGNANCY, EMBRYO-FETUS

FIBRINOGEN

- SEE BLOOD COAGULATION, FIBRINOGEN

FIBRINOGENASE

- SEE BLOOD COAGULATION, THROMBIN

FIBROBLASTS

- SEE CONNECTIVE TISSUE CELLS, FIBROBLASTS

FIBROGENESIS

- SEE CONNECTIVE TISSUE DEVELOPMENT, FIBROGENESIS

FIBRONECTIN

- SEE GLYCOPROTEINS, FIBRONECTIN

FIBROSARCOMA

- SEE NEOPLASMS, FIBROSARCOMA

FIBROSIS

- SEE METABOLIC DISORDERS INBORN, CYSTIC FIBROSIS

FISH*

- ** R01DE-05555-01 Cell migration in the teleost embryo

FIXED ACTION PATTERN (ANIMAL BEHAVIOR)

- SEE PSYCHOLOGY, BEHAVIOR ANIMAL

FIXED CHARGE HYPOTHESIS

- SEE BIOLOGICAL TRANSPORT, PASSIVE TRANSPORT, DIFFUSION

FLAGELLAR MOVEMENT

- SEE CELL COMPONENTS, CILIARY AND FLAGELLAR MOVEMENT

FLAGYL

- SEE IMIDAZOLES, METRONIDAZOLE

FLAVOR (SENSE)

- SEE SENSORY-PERCEPTUAL PROCESSES, TASTE

FLUID FLOW

- SEE PHYSICAL PROPERTIES, FLUID FLOW

FLUIDS

- SEE BODY FLUIDS (AND RELATED SUBSTANCES)

FLUORESCENCE LABELING, PROBES

- SEE DYES, FLUORESCENT DYES AND PROBES

FLUORESCENT ANTIBODY TECHNIQUE

- SEE IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOFLOURESCENCE*

FLUORESCENT ANTIGEN TECHNIQUE

- SEE IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOFLOURESCENCE*

FLUORESCENT DYES

- SEE DYES, FLUORESCENT DYES AND PROBES

FLUORIDE INGESTED

- SEE DENTAL DISORDERS CHEMOTHERAPY, FLUORIDE INGESTED

FLUORIDE TREATMENTS (TOPICAL)

- SEE DENTAL DISORDERS CHEMOTHERAPY, FLUORIDE TREATMENTS (TOPICAL)

FLUORIDES

- SEE HALOGENS, FLUORINE (COMPOUNDS) SEE ALSO SPECIFICS

FLUORINE (COMPOUNDS)

- SEE HALOGENS, FLUORINE (COMPOUNDS) SEE ALSO SPECIFICS

FLUOROCARBON POLYMERS

- SEE PLASTICS, FLUOROCARBON POLYMERS

FLUOROXYCARBONS (GENERAL)

- SEE HALOXYCARBONS, FLUOROXYCARBONS (GENERAL)

FLUOROSIS

- SEE HALOGEN POISONING, FLUOROSIS

FLUOROURACIL

- SEE HALOPYRIMIDINES, HALDURACIL, FLUOROURACIL

FOAMING AGENTS

- SEE PHYSICAL PROPERTIES, SURFACTANTS

FOLIC ACID ANTAGONISTS, METHOTREXATE

- R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

FOLLICLE STIMULATING HORMONE-RELEASE INHIBITING FACTOR

- SEE PITUITARY-DIENCEPHALON HORMONES, SOMATOSTATIN

FOLLICULIBERIN

- SEE PITUITARY-DIENCEPHALON HORMONES, SOMATOSTATIN

FOLLOW-UP STUDY

- SEE POPULATION STUDIES HUMAN, LONGITUDINAL STUDY

FOLLOW-UP STUDY, ANIMAL

- SEE POPULATION STUDIES ANIMAL, LONGITUDINAL STUDY

FOOD

- SEE ALSO GROWTH MEDIA
SEE ALSO NUTRITION (GENERAL)

- ** P01DE-01850-18 0071 Nutritional sources and metabolic roles of fluoride - Fluoride content of infant, toddler and adult foods

- R01DE-05112-03 Muscle activity and control in mastication (mammals, lizards)

- ** N01DE-12434-00 Identify cariogenic elements of food

FOOD, ANIMAL FEEDS

- R01DE-06000-01 Effect of parotid function on saliva and cells

FOOD, BEVERAGES

- N01DE-12434-00 Identify cariogenic elements of food

FOOD, DAIRY PRODUCTS

- SEE ALSO BODY FLUIDS, MILK
P01DE-01850-18 0085 Nutritional sources and metabolic roles of fluoride - Absorption of fluoride from dietary substances (rats)
R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)
N01DE-12434-00 Identify cariogenic elements of food

FOOD, INFANT FOODS

- ** P01DE-01850-18 0071 Nutritional sources and metabolic roles of fluoride - Fluoride content of infant, toddler and adult foods

- ** P01DE-01850-18 0085 Nutritional sources and metabolic roles of fluoride - Absorption of fluoride from dietary substances (rats)

- N01DE-12434-00 Identify cariogenic elements of food

FOOD, MEAT

- N01DE-12434-00 Identify cariogenic elements of food

FOOD, POULTRY PRODUCTS

- N01DE-12434-00 Identify cariogenic elements of food

FOOD, SEAFOOD

- N01DE-12434-00 Identify cariogenic elements of food

FOOD, SWEETENING AGENTS

- ** N01DE-02427-04 Synthesize noncariogenic sweeteners
** N01DE-02428-04 Synthesis of noncariogenic sweeteners (mice)

- ** R01DE-05466-03 Biochemical studies of a sweetener, SRI Oxime V (rats, mice, dogs, monkeys)

- ** R01DE-05476-02 Novel peptide derived sweeteners
N01DE-12434-00 Identify cariogenic elements of food

FOOD ADDITIVES

- SEE FOOD SCIENCES AND TECHNOLOGY, FOOD ADDITIVES

FOOD ANALYSIS (CHEMICAL CONSTITUENTS)

- SEE NUTRITION, DIETARY CONSTITUENTS (GENERAL)

FOOD CONSTITUENTS

- SEE NUTRITION, DIETARY CONSTITUENTS (GENERAL)

FOOD CONTAMINATION

- SEE FOOD SCIENCES AND TECHNOLOGY, FOOD SANITATION, FOOD CONTAMINATION

FOOD PREPARATION

- SEE FOOD SCIENCES AND TECHNOLOGY, FOOD PROCESSING AND PREPARATION

FOOD PROCESSING

- SEE FOOD SCIENCES AND TECHNOLOGY, FOOD PROCESSING AND PREPARATION

FOOD QUALITY

- SEE FOOD SCIENCES AND TECHNOLOGY, FOOD QUALITY-STANDARDS

FOOD REQUIREMENTS DIETARY

- SEE NUTRITIONAL REQUIREMENTS

FOOD SCIENCES AND TECHNOLOGY, DEHYDRATED FOODS

- N01DE-12434-00 Identify cariogenic elements of food

FOOD SCIENCES AND TECHNOLOGY, FOOD ADDITIVES

- SEE ALSO FOOD, SWEETENING AGENTS
SEE ALSO OXIDANTS, ANTIOXIDANTS
N01DE-12434-00 Identify cariogenic elements of food

FOOD SCIENCES AND TECHNOLOGY, FOOD PROCESSING AND PREPARATION

- P01DE-01850-18 0082 Nutritional sources and metabolic roles of fluoride - Nonionic fluoride in foods (human)
N01DE-12434-00 Identify cariogenic elements of food

FOOD SCIENCES AND TECHNOLOGY, FOOD QUALITY-STANDARDS

- ** R01DE-05466-03 Biochemical studies of a sweetener, SRI Oxime V (rats, mice, dogs, monkeys)

FOOD SCIENCES AND TECHNOLOGY, FOOD SANITATION, FOOD CONTAMINATION

- ** P01DE-01850-18 0082 Nutritional sources and metabolic roles of fluoride - Nonionic fluoride in foods (human)

FOOD SCIENCES AND TECHNOLOGY, SYNTHETIC FOODS

- ** N01DE-02427-04 Synthesize noncariogenic sweeteners
** N01DE-02428-04 Synthesis of noncariogenic sweeteners (mice)

FOODS INTERACTION WITH PHYSICAL OR CHEMICAL AGENTS

- SEE NUTRIENTS AND PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

(contd.)

FORAMEN OVALE (HEART) PATENT

SEE CONGENITAL ABNORMALITIES, HEART SEPTAL DEFECTS

FOREBRAIN

SEE BRAIN, PROSENCEPHALON (GENERAL)

FOREIGN LANGUAGES

SEE INFORMATION AND COMMUNICATION, LANGUAGES, FOREIGN

FORMALDEHYDE

SEE ALDEHYDES, FORMALDEHYDE

FORMANILIDE

SEE PHENYLAMIDES

FRACTIONATION (GENERAL)

SEE PHYSICAL SEPARATION, FRACTIONATION (GENERAL)*

FRACTURE FIXATION

SEE SKELETAL DISORDERS, ORTHOPEDICS, FRACTURE FIXATION

FRACTURES

SEE INJURIES, FRACTURES

FREQUENCY INTERVAL OF STIMULUS

SEE STIMULUS INTERVAL

BETA-FRUCTOFURANOSIDASE

SEE CARBOHYDRASES, BETA-FRUCTOFURANOSIDASE

FRUCTOSE

SEE HEXOSES, FRUCTOSE

FUNCTION, BODILY ORGANS

SEE MUSCLE FUNCTION

SEE RESPIRATORY FUNCTION

FUNCTIONAL GROUPS (CHEMISTRY)

SEE CHEMICAL REACTION SITES, FUNCTIONAL GROUPS

FUSION FAILURES, CONGENITAL

SEE CONGENITAL ABNORMALITIES, FUSION FAILURES

FUSOBACTERIA

SEE BACTERIA, BACTEROIDACEAE, FUSOBACTERIA*

GAMMA GLOBULINS 7S

SEE GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN G

GAMMA GLOBULINS 19S

SEE GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN M

GANGLIA NERVOUS SYSTEM

SEE NERVOUS SYSTEM, GANGLIA

GARGOYLISM

SEE METABOLIC DISORDERS INBORN, MUCOPOLYSACCHARIDOSIS, LIPOCHONDRODYSSTROPHY

GASTRIC FEEDING

SEE NUTRITION, DIET SCHEDULE AND ROUTE, TUBE FEEDING

GASTRIC INTUBATION (FEEDING)

SEE NUTRITION, DIET SCHEDULE AND ROUTE, TUBE FEEDING

GASTROINTESTINAL ABSORPTION-TRANSPORT

SEE GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT (GENERAL)

GASTROINTESTINAL AGENTS, DIGESTANTS (GENERAL)

R01DE-06000-01 Effect of parotid function on saliva and cells

GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT (GENERAL)

R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)

R01DE-06113-01 Determinants of fluoride in the oral environment (Dogs, rats)

GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT, DIETARY NUTRIENTS

P01DE-01850-18 0085 Nutritional sources and metabolic roles of fluoride - Absorption of fluoride from dietary substances (rats)

R01DE-05466-03 Biochemical studies of a sweetener, SRI Oxime V (rats, mice, dogs, monkeys)

GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT, DRUGS

P01DE-01850-18 0072 Nutritional sources and metabolic roles of fluoride - Effect of fluoride on iron transport (mice)

P01DE-01850-18 0075 Nutritional sources and metabolic roles of fluoride - Metabolic handling of perfluorooctanoic acid (rats)

** P01DE-01850-18 0085 Nutritional sources and metabolic roles of fluoride - Absorption of fluoride from dietary substances (rats)

P01DE-01850-18 0086 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on serum alkaline phosphatase activity (mice)

P01DE-01850-18 0087 Nutritional sources and metabolic roles of fluoride - Methodology for determining ionic fluoride content of human plasma

** P01DE-01850-18 0089 Nutritional sources and metabolic roles of fluoride - Effect of skeletal fluoride load on retention of administered fluoride

GASTROINTESTINAL FUNCTION, DEGLUTITION

R01DE-05728-01 Role of chemoreceptors in craniofacial function (lambs)

** R01DE-05738-01 Mastication, food transport, and swallowing in primates

GASTROINTESTINAL SYSTEM (GENERAL)

R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

GASTROINTESTINAL SYSTEM, INTESTINES

R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

GASTROINTESTINAL SYSTEM, INTESTINES, SMALL INTESTINE, DUODENUM

P50DE-02670-15 0035 Institute of Dental Research - Granulocyte growth and division

GENE CLONING

SEE NUCLEIC ACIDS CLONING

GENE DOSAGE

SEE GENETICS, GENES, GENE DOSAGE

GENE EXPRESSION

SEE GENETICS, GENES, GENE EXPRESSION

GENE INSERTION INTO FOREIGN HOSTS

SEE GENETIC MANIPULATION

GENE MUTATION

SEE GENETICS, MUTATION, GENE MUTATION

GENE SPLICING (GENETIC MANIPULATION)

SEE GENETIC MANIPULATION

GENERAL MEDICINE STUDY SECTION

** R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

GENERAL MEDICINE A STUDY SECTION

** R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)

** R01DE-04660-06 Keratohyalin in keratinization-Oral mucosa and skin (human)

GENERAL MEDICINE B STUDY SECTION

** R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)

** R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)

** R01DE-05209-04 Metabolic pathways in bone

** R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)

** R01DE-05249-02 Salivary secretion-role of calcium (mice)

** R01DE-05467-02 Pathogenesis of localized bone destruction

** R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

** R01DE-06065-01 The role of lymphoid cells in alveolar bone resorption

GENES CONTROLLING HISTOCOMPATIBILITY ANTIGENS (ISOALLOANTIGENS)

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

GENETIC CODING

SEE GENETICS, GENETIC CODING

GENETIC DISORDERS (SEE ALSO APPROPRIATE CONGENITAL ABNORMALITIES)

SEE ALSO CONGENITAL ABNORMALITIES

SEE ALSO DISEASE PRONESS-RISK

SEE ALSO GENETICS, MUTATION

SEE ALSO METABOLIC DISORDERS INBORN

P01DE-02872-12 0055 Craniofacial dysmorphology - Human genetics

GENETIC DISORDERS, DOWN'S SYNDROME

R01DE-05078-05 Craniofacial growth and remodeling (human)

GENETIC DISORDERS, METABOLIC ERRORS

SEE METABOLIC DISORDERS INBORN

GENETIC DISORDERS, SEX-LINKED CONDITIONS

R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

GENETIC ENGINEERING

SEE GENETIC MANIPULATION

GENETIC MANIPULATION

SEE ALSO NUCLEIC ACIDS CLONING

P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)

P50DE-02670-15 0033 Institute of Dental Research - Genetic and biochemical basis for S mutants virulence (rats)

R01DE-03258-10 Streptococcus mutans-Dental caries mechanism (human)

R01DE-03658-17 Genetic polymorphisms of saliva (human)

R01DE-04224-07 Genetics of oral microflora

GENETIC MAPPING

R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)

GENETIC MAPPING, GENETIC MARKERS

R01DE-03658-17 Genetic polymorphisms of saliva (human)

R01DE-05758-01 Genetic linkage study of cleft lip-palate in Denmark

R01DE-05771-01 Quantitative dental traits in man-Major gene effects

GENETIC MAPPING, LINKAGE

R01DE-03658-17 Genetic polymorphisms of saliva (human)

R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)

** R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

** R01DE-05758-01 Genetic linkage study of cleft lip-palate in Denmark

R01DE-05771-01 Quantitative dental traits in man-Major gene effects

GENETIC MARKERS

SEE GENETIC MAPPING, GENETIC MARKERS

GENETIC REGULATION

SEE GENETICS, GENETIC REGULATION

GENETIC STRAINS

SEE BIOLOGY, SYSTEMATIC, GENETIC STRAINS

GENETICS

SEE ALSO CELL DIVISION

SEE ALSO IMMUNOGENETICS (GENERAL)

SEE ALSO MAMMALIAN GENETICS STUDY SECTION

SEE ALSO NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)

SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOIMMUNITY

** P01DE-02872-12 0055 Craniofacial dysmorphology - Human genetics

GENETICS, CHROMOSOMES, CHROMATIN

R01DE-04511-06 Stability of differentiation-Craniofacial study (human, hamsters)

GENETICS, CYTOGENETICS

SEE ALSO CELL DIVISION, MITOSIS

** P50DE-02600-15 0040 Support for oral biology research center - Fate of actinomyces viscosus components within phagocytic cells

R01DE-04039-04 Sex steroid metabolism in oral tissues

R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)

R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

** N01DE-52452-12 Oral facial malformations in the rhesus monkey

GENETICS, DEVELOPMENTAL GENETICS

SEE ALSO CONGENITAL ABNORMALITIES

SEE ALSO GENETIC DISORDERS (SEE ALSO APPROPRIATE CONGENITAL ABNORMALITIES)

SEE ALSO METABOLIC DISORDERS INBORN

SEE ALSO PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)

** P50DE-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)

** R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)

** R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

R01DE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)

** R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)

** R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)

** R01DE-05041-03 Orofacial anomalies in phenytoin teratogenesis (mice, human)

** R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

** R01DE-05367-02 Cranio-facial anomalies in the oel mouse

** R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)

** N01DE-52452-12 Oral facial malformations in the rhesus monkey

GENETICS, EXTRACHROMOSOMAL INHERITANCE

R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)

GENETICS, EXTRACHROMOSOMAL INHERITANCE, PLASMIDS

P50DE-02623-14 0005 Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria

** P50DE-02731-15 0019 Development support for dental research institute - Structure and maintenance of extrachromosomal DNA in streptococci

** R01DE-04224-07 Genetics of oral microflora

R01DE-05141-03 Cariogenic mechanisms of gingival plaque bacteria

R01DE-05218-03 DNA homologies among bacteria of periodontal diseases

** R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)

GENETICS, GENES, ALLELES

R01DE-05322-01 Genetic analysis of birth defects involving septa (human, mice)

(contd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

GENETICS, GENES, GENE DOSAGE

- R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

GENETICS, GENES, GENE EXPRESSION

SEE ALSO GENETICS, GENOTYPES

- ** P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
- P50DE-02600-15 0040 Support for oral biology research center - Fate of actinomycetes viscosus components within phagocytic cells
- R01DE-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)
- ** R01DE-03658-17 Genetic polymorphisms of saliva (human)
- R01DE-04039-04 Sex steroid metabolism in oral tissues
- R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)
- R01DE-04511-06 Stability of differentiation--Craniofacial study (human, hamsters)
- R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)
- R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)
- R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)
- R01DE-05218-03 DNA homologies among bacteria of periodontal diseases
- R01DE-05367-02 Cranio-facial anomalies in the oel mouse
- ** R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)
- R01DE-05512-02 Role of macrophages in periodontal disease
- R01DE-05684-01 Saliva proteins--Chemistry, genetics and oral health
- ** R01DE-05771-01 Quantitative dental traits in man--Major gene effects

GENETICS, GENES, GENE EXPRESSION, PLEIOTROPISM

- R01DE-05771-01 Quantitative dental traits in man--Major gene effects

GENETICS, GENETIC CODING

SEE ALSO GENETICS, GENETIC REGULATION, GENETIC INDUCTION-REPRESSION-DEREPRESSION, TRANSCRIPTION

SEE ALSO GENETICS, GENETIC REGULATION, GENETIC INDUCTION-REPRESSION-DEREPRESSION, TRANSLATION

SEE ALSO PROTEINS BIOSYNTHESIS

- R01DE-03258-10 Streptococcus mutans--Dental caries mechanism (human)
- R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)

GENETICS, GENETIC REGULATION

- R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
- R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)

GENETICS, GENETIC REGULATION, GENETIC INDUCTION-REPRESSION-DEREPRESSION, TRANSCRIPTION

- R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)

GENETICS, GENETIC REGULATION, GENETIC INDUCTION-REPRESSION-DEREPRESSION, TRANSLATION

- R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)

GENETICS, GENOTYPES

- R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- ** R01DE-05669-01 Chorion type and dental morphology in twins

GENETICS, GENOTYPES, HETEROZYGOTES

- P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)

GENETICS, MICROBIAL

SEE ALSO GENETICS, POPULATION GENETICS MICROORGANISMS

SEE ALSO NUCLEIC ACIDS, DNA BACTERIAL

SEE ALSO REPRODUCTION MICROORGANISMS

- P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
- ** P50DE-02600-15 0040 Support for oral biology research center - Fate of actinomycetes viscosus components within phagocytic cells
- P50DE-02670-15 0033 Institute of Dental Research - Genetic and biochemical basis for S mutans virulence (rats)
- R01DE-03258-10 Streptococcus mutans--Dental caries mechanism (human)
- R01DE-03758-07 Virulence characterization and immunization against S mutans (rats, rabbits)
- ** R01DE-04224-07 Genetics of oral microflora
- R01DE-04529-05 Replacement therapy of dental caries (rats, monkeys)
- R01DE-04645-04 A genetic-biochemical analysis of spirochete motility
- ** R01DE-05218-03 DNA homologies among bacteria of periodontal diseases

- ** R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)
- N01DE-62491-12 Use of mutants of cariogenic streptococci to prevent dental caries (rats)

GENETICS, MUTAGENS, MUTAGEN TESTS

- R01DE-03758-07 Virulence characterization and immunization against S mutans (rats, rabbits)
- R01DE-05102-04 Potential anti-carries agents (rats)

GENETICS, MUTATION

- R01DE-03758-07 Virulence characterization and immunization against S mutans (rats, rabbits)
- R01DE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)

GENETICS, MUTATION, GENE MUTATION

SEE ALSO GENETICS, GENES, GENE EXPRESSION, PLEIOTROPISM

- ** R01DE-05367-02 Cranio-facial anomalies in the oel mouse

GENETICS, MUTATION, MUTANTS*

SEE ALSO BIOLOGY, SYSTEMATIC, GENETIC STRAINS

- ** P50DE-02670-15 0025 Institute of Dental Research - Biochemical basis for the cariogenic property of Streptococcus mutans (rat)
- R01DE-04529-05 Replacement therapy of dental caries (rats, monkeys)
- R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

GENETICS, PHARMACOGENETICS*

- R01DE-05459-02 Phenytoin--Pathogenesis of gingival overgrowth (cats)

- ** N01DE-52452-12 Oral facial malformations in the rhesus monkey

GENETICS, POPULATION GENETICS, INBREEDING

- P50DE-02668-15 0213 Regional dental research center - Hormone action is the salivary glands of inbred mice

GENETICS, POPULATION GENETICS HUMAN

- R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
- R01DE-03658-17 Genetic polymorphisms of saliva (human)

GENETICS, POPULATION GENETICS MICROORGANISMS

- ** R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)

GENETICS, RECOMBINATION

- R01DE-05190-03 Factors determining variation in adult oral mucosa

GENETICS STUDY SECTION

- ** R01DE-04224-07 Genetics of oral microflora
- ** R01DE-05322-01 Genetic analysis of birth defects involving septa (human, mice)

GENOTYPES

SEE GENETICS, GENOTYPES

GEOGRAPHICAL SITES, EUROPE, SCANDINAVIAN COUNTRIES

- ** P01DE-01850-18 0087 Nutritional sources and metabolic roles of fluoride - Methodology for determining ionic fluoride content of human plasma
- ** R01DE-05758-01 Genetic linkage study of cleft lip-palate in Denmark

GEOGRAPHICAL SITES, UNITED STATES

- P01DE-01850-18 0071 Nutritional sources and metabolic roles of fluoride - Fluoride content of infant, toddler and adult foods
- ** P01DE-01850-18 0087 Nutritional sources and metabolic roles of fluoride - Methodology for determining ionic fluoride content of human plasma

GERIATRICS

SEE AGING

GERM-FREE

SEE COMMUNICABLE DISEASE CONTROL, GERM-FREE

GERM LAYERS

SEE EMBRYOLOGY, GERM LAYERS

GERMICIDES, THERAPEUTIC

SEE COMMUNICABLE DISEASE CONTROL AGENTS

GERONTOLOGY

SEE AGING

GINGIVA

SEE DENTAL STRUCTURE, GINGIVA

GINGIVAL CURETTAGE

SEE DENTISTRY, SUBGINGIVAL CURETTAGE

GINGIVAL DISORDERS

SEE DENTAL DISORDERS, GINGIVAL

GINGIVAL HYPERPLASIA

SEE DENTAL DISORDERS, GINGIVAL HYPERPLASIA

GINGIVAL SULCUS

SEE DENTAL STRUCTURE, GINGIVA, GINGIVAL SULCUS

GINGIVITIS

SEE DENTAL DISORDERS, GINGIVITIS

GLANDS

SEE ENDOCRINOLOGY, ENDOCRINES

SEE ORAL-PHARYNGEAL, SALIVARY GLANDS

SEE TISSUE, EXOCRINE GLANDS (GENERAL)

GLASS

SEE SILICATES, GLASS

GLOBULINS

SEE ALSO PLANTS PROTEINS, LECTINS, CONCAVALIN A

R01DE-04039-04 Sex steroid metabolism in oral tissues

GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN(S)

SEE ALSO IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL

SEE ALSO IMMUNOLOGY, ANTIBODIES

SEE ALSO IMMUNOLOGY, ANTIBODIES, ANTIBODY RECEPTORS

- ** P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
- P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction
- R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)
- R01DE-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)
- R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)
- R01DE-05531-03 Salivary immune factors (human, bacteria)

GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN A

SEE ALSO IMMUNOLOGY, SECRETORY (ANTIBODY) (FACTOR) SYSTEM

- R01DE-01554-20 Host factors in caries resistance (human, rats)
- P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction
- ** P50DE-02670-15 0018 Institute of Dental Research - Structure of human secretory immunoglobulin A
- R01DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins
- R01DE-04614-05 Adherence of oral streptococci to hydroxyapatite
- P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)
- R01DE-05414-02 The local immune response in periodontal disease (human)
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05626-01 Role of complement in periodontal disease
- R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)
- ** R23DE-05789-01 IgA receptor bearing oral cells in cystic fibrosis (human)
- N01DE-12430-00 Investigation of anticaries vaccine in primates

GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN D

R01DE-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)

P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)

R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN E

P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)

GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN G

P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)

P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations

R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)

R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)

R01DE-05330-02 Herpes virus antibodies in patients with oral cancer

R01DE-05414-02 The local immune response in periodontal disease (human)

R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

R01DE-05531-03 Salivary immune factors (human, bacteria)

R01DE-05626-01 Role of complement in periodontal disease

R01DE-05690-01 Localization of the procollagens in dental tissues

R01DE-05696-01 Streptococcus mutans interaction with animal tissue (also human)

N01DE-12430-00 Investigation of anticaries vaccine in primates

GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN M

P50DE-02670-15 0018 Institute of Dental Research - Structure of human secretory immunoglobulin A

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

(contd.)

- P500E-04898-05 0001 Periodontal disease research center - Microbiology (human)
 R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)
 R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
 N01DE-12430-00 Investigation of anticaries vaccine in primates

GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN BIOSYNTHESIS

- SEE ALSO IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL
 R01DE-05414-02 The local immune response in periodontal disease (human)
 R01DE-05723-01 Spirochete influence on immunity in oral disease

GLOMERULUS

- SEE KIDNEY, GLOMERULUS

ALPHA1,4-GLUCAN GLUCOHYDROLASE

- SEE CARBOHYDRASES, ALPHA 1,4-GLUCAN GLUCOHYDROLASE

GLUCANS

- SEE HEXOSANS, GLUCANS

D-GLUCITOL

- SEE SUGAR ALCOHOLS, HEXITOLS, D-GLUCITOL

GLUCOAMYLASE

- SEE CARBOHYDRASES, ALPHA 1,4-GLUCAN GLUCOHYDROLASE

GLUCOCORTICOIDS

- SEE ADRENAL CORTEX HORMONES, GLUCOCORTICOIDS

ALPHA-D-GLUCOPYRANOSYL-BETA-D-FRUCTOFURANOSIDE

- SEE DISACCHARIDES, SUCROSE

GLUCOSAMINOGLYCANS

- SEE POLYSACCHARIDES, GLYCOSAMINOGLYCANS

GLUCOSE

- SEE HEXOSES, GLUCOSE

D-GLUCOSE

- SEE HEXOSES, GLUCOSE

GLUCOSE METABOLISM

- SEE CARBOHYDRATES METABOLISM, GLUCOSE METABOLISM

GLUCOSE TRANSPORT

- SEE CARBOHYDRATES TRANSPORT, GLUCOSE TRANSPORT

4(ALPHA-D-GLUCOSIDO)-D-GLUCOSE

- SEE DISACCHARIDES, MALTOSE

GLUCURONOSYLTRANSFERASES

- SEE GLYCOSYLTRANSFERASES, GLUCURONOSYLTRANSFERASES

GLUES

- SEE CONSUMER PRODUCTS, GLUES AND ADHESIVES

L-GLUTAMATE:AMMONIA LIGASE (ADP)

- SEE ACID-AMMONIA LIGASES, L-GLUTAMATE:AMMONIA LIGASE (ADP)

GLUTAMATES

- SEE DICARBOXYLIC AMINO ACIDS, GLUTAMATES

GLUTAMINE SYNTHETASE

- SEE ACID-AMMONIA LIGASES, L-GLUTAMATE:AMMONIA LIGASE (ADP)

GLYCERIC ACID DIPHOSPHATES

- SEE TRIOSE ACIDS, GLYCERIC ACID DIPHOSPHATES

GLYCERIN

- SEE TRIOSE ALCOHOLS, GLYCERIN

GLYCEROL

- SEE TRIOSE ALCOHOLS, GLYCERIN

GLYCOGENESIS

- SEE CARBOHYDRATES BIOSYNTHESIS

GLYCOLIPIDS

- R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
 R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)
 R01DE-04957-03 Bacterial metabolites in oral diseases
 R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)
 R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)

GLYCOLYSIS

- SEE HEXOSES, GLYCOLYSIS

GLYCOPROTEINS

- SEE ALSO CARBOHYDRATES, PROTEIN BOUND CARBOHYDRATES
 SEE ALSO PROTEOGLYCANS

- R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
 R01DE-01554-20 Host factors in caries resistance (human, rats)
 ** R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
 P500E-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus
 P500E-02668-15 0158 Regional dental research center - Thrombin-platelet interactions (human)

- P500E-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins

- P500E-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues

- P01DE-02847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria

- R01DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)

- R01DE-03301-11 Connective tissue of the periodontium--Collagen maturation

- R01DE-03731-06 Dextran sucrose of Streptococcus sanguis

- R01DE-03915-08 Tooth-saliva interface phenomena and dental canines (rabbits, goats)

- R01DE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)

- R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)

- ** R01DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins

- R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)

- R01DE-04971-03 Human salivary antigens--Characterization (monkeys)

- R01DE-05092-03 Proteins involved in dentinogenesis

- R01DE-05251-02 Salivary gland secretory mechanisms (rats)

- R01DE-05427-01 Adherence mechanisms of oral microbes

- R23DE-05429-03 Adherence of periodontal disease-associated bacteria

- R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)

- R01DE-05483-02 Characterization of predental extracellular fluid (rats)

- R01DE-05684-01 Saliva proteins--Chemistry, genetics and oral health

GLYCOPROTEINS, FIBRONECTIN

- R01DE-05379-01 Morphogenesis and maturation of craniofacial sutures (animals)

- R01DE-05630-01 Matrix/cell surface in neural crest cell morphogenesis (mice, chick, quail)

GLYCOSAMINOGLYCANS

- SEE POLYSACCHARIDES, GLYCOSAMINOGLYCANS

GLYCOSIDASES

- SEE CARBOHYDRASES

GLYCOSIDE HYDROLASES

- SEE CARBOHYDRASES

GLYCOSYLTRANSFERASES

- P500E-02670-15 0024 Institute of Dental Research - Metabolism of connective tissue proteoglycans

- P500E-02670-15 0025 Institute of Dental Research - Biochemical basis for the cariogenic property of Streptococcus mutans (rat)

- R01DE-03258-10 Streptococcus mutans--Dental caries mechanism (human)

- ** R01DE-03739-09 Glycosyltransferases from oral bacteria (bacteria)

- R01DE-05102-04 Potential anti-caries agents (rats)

GLYCOSYLTRANSFERASES, GLUCURONOSYLTRANSFERASES

- R01DE-03118-11 Inhibition of saccharide metabolism by oral flora

- R01DE-03758-07 Virulence characterization and immunization against S mutans (rats, rabbits)

GMP CYCLIC

- SEE PURINE NUCLEOTIDES, GUANINE NUCLEOTIDES, GMP CYCLIC

GNOTOBIOTICS

- SEE COMMUNICABLE DISEASE CONTROL, GERM-FREE

GOLD

- SEE METALS, HEAVY METALS, GOLD (COMPOUNDS)

GONADOTROPINS

- SEE REPRODUCTIVE HORMONES, GONADOTROPINS

GORETEX

- SEE PLASTICS, FLUOROCARBON POLYMERS

GPI-A LOCUS (GUINEA PIG)

- SEE IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)

GRAFT VERSUS HOST REACTION GENES

- SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

GRAFT VERSUS HOST REACTIONS

- SEE TISSUE COMPATIBILITY-TRANSPLANT, GRAFT VERSUS HOST REACTIONS

GRAFTS

- SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION

GRAM-NEGATIVE ANAEROBIC BACTERIA

- SEE BACTERIA, ACTINOMYCETALES, LEPTOTRICHIA*

GRAM-NEGATIVE ANAEROBIC COCCI

- SEE BACTERIA, NEISSERIAE, VEILLONELLA*

GRAM-NEGATIVE BACTERIA

- SEE BACTERIA, GRAM-NEGATIVE*

GRAM-NEGATIVE FACULTATIVELY ANAEROBIC RODS

- SEE BACTERIA, PSEUDOMONADALES, VIBRIO*

GRAM-POSITIVE BACTERIA

- SEE BACTERIA, GRAM-POSITIVE*

GRANULOCYTES (GENERAL)

- SEE BLOOD CELLS, LEUKOCYTES, GRANULOCYTES (GENERAL)

GROWTH ABNORMAL, KERATINIZATION

ABNORMAL

- R01DE-05525-02 Nature of the permeability barrier in oral epithelium

GROWTH AND DEVELOPMENT

- SEE ALSO CELL DIVISION

- SEE ALSO CELL GROWTH REGULATION

- SEE ALSO CHILD DEVELOPMENT (NON-PSYCHOLOGICAL)

- SEE ALSO CHILD MENTAL DEVELOPMENT

- SEE ALSO GENETICS, DEVELOPMENTAL GENETICS

- SEE ALSO GROWTH MICROORGANISMS

- SEE ALSO NEOPLASTIC GROWTH

- SEE ALSO NUTRITION, DEVELOPMENTAL NUTRITION

- SEE ALSO POPULATION STUDIES CELL

- P500E-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel

- M P01DE-03610-15 Cranio-facial growth and development

- R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)

- ** R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years

- ** R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)

- R01DE-04990-03 Normal and abnormal faces (human)

- R23DE-05037-03 Biochemical role of zinc in teeth and bones

- ** R23DE-05142-03 Control mechanisms in salivary gland development (rats)

- ** R01DE-05145-03 Adjustive cranial skeletal growth (rats)

- ** R23DE-05232-03 Growth and function of the muscles of mastication (monkeys)

- R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)

- R01DE-05531-03 Salivary immune factors (human, bacteria)

- ** R23DE-05627-02 Effects of mechanical forces on craniofacial growth (monkeys, rabbits)

- ** R01DE-05632-01 Development of salivary gland secretory function (rats)

- ** R01DE-05868-01 Multivariate analysis of craniofacial growth in clefting

GROWTH AND DEVELOPMENT, HISTOGENESIS

- SEE ALSO CARDIOVASCULAR SYSTEM, ANGIOGENESIS

- SEE ALSO CELL-CELL INTERACTION, CELL AGGREGATION

- SEE ALSO CELL DIFFERENTIATION

- SEE ALSO CONGENITAL ABNORMALITIES

- SEE ALSO CONNECTIVE TISSUE DEVELOPMENT

- SEE ALSO DENTAL DEVELOPMENT

- SEE ALSO MUSCLES, MYOGENESIS

- SEE ALSO NEUROLOGY, DEVELOPMENTAL, NEUROGENESIS

- SEE ALSO SKELETAL SYSTEM, BONE DEVELOPMENT

- SEE ALSO SKELETAL SYSTEM, CARTILAGE DEVELOPMENT

- P01DE-01697-19 0040 A research program in craniofacial problems - Pattern recognition for reconstruction of nasal capsular anatomy

- R01DE-02110-17 Salivary gland structure and function (rats)

- M P01DE-02848-11 Biology of connective tissue, bones, and teeth

- ** P01DE-02848-11 0003 Biology of connective tissue, bones, and teeth - Mandibular morphogenesis--Embryonic neonatal and postnatal development (mice)

- P01DE-02848-11 0004 Biology of connective tissue, bones, and teeth - Embryonic basal lamina development

- ** R01DE-03715-06 Cellular assembly--Its role in facial morphogenesis (fungi)

- ** R01DE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)

- ** R01DE-04731-05 Analysis of primary palate formation (chick embryo)

- R01DE-04897-02 Functional development of salivary glands (rats)

- ** R01DE-05135-03 Osteoclast origin and histogenesis in periodontium (rats)

- ** R01DE-05138-03 Visceral arches and oro-facial morphogenesis (mice, monkeys)

- R01DE-05323-02 Calcium transport in developing dental tissues (frogs, rats)

- ** R01DE-05367-02 Cranio-facial anomalies in the oel mouse

- ** R01DE-05379-01 Morphogenesis and maturation of craniofacial sutures (animals)

- ** R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)

- ** R01DE-05630-01 Matrix/cell surface in neural crest cell morphogenesis (mice, chick, quail)

- ** R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)

- ** R01DE-05838-02 Morphogenetic role of glycosaminoglycans (chick embryo)

- R01DE-05999-01 The role of nutrition in oral health

- (contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

GROWTH AND DEVELOPMENT, KERATINIZATION

- ** P50DE-02600-15 0032 Support for oral biology research center - Keratohyalin in keratinization of oral mucosa and skin (human, rats)
- P50DE-02731-15 0032 Development support for dental research institute - Epithelial cell basal lamina biosynthesis (rats)
- R01DE-03934-07 Differentiation of oral epithelium (rats)
- ** R01DE-04660-06 Keratohyalin in keratinization--Oral mucosa and skin (human)
- R23DE-05887-01 Effects of oral bacteria on epithelium in vitro

GROWTH AND DEVELOPMENT, REGENERATION

- SEE ALSO INJURIES, WOUND HEALING
- SEE ALSO NERVOUS SYSTEM REGENERATION
- SEE ALSO SKELETAL SYSTEM REGENERATION
- SEE ALSO SKELETAL SYSTEM REGENERATION, BONE REGENERATION
- ** P50DE-02731-15 0033 Development support for dental research institute - Clinical trials of periodontal therapy
- ** R23DE-05072-03 Stimulation of regenerating rat submandibular glands
- ** R01DE-05190-03 Factors determining variation in adult oral mucosa
- R01DE-05395-02 Stem cells in oral mucosa
- ** R23DE-05491-02 Control of biomineralization in two species (snails)
- ** R01DE-05838-02 Morphogenetic role of glycosaminoglycans (chick embryo)

GROWTH DISORDERS POSTNATAL (SEE ALSO APPROPRIATE SPECIFICS)

- SEE ALSO PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)
- SEE ALSO SKELETAL DISORDERS, BONE DEVELOPMENT
- P01DE-02872-12 0061 Craniofacial dysmorphology - Craniofacial dysmorphology
- ** R01DE-05078-05 Craniofacial growth and remodeling (human)
- R01DE-05215-03 Influences on stability following orthognathic surgery

GROWTH DISORDERS PRENATAL

- SEE PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)

GROWTH FACTOR NERVE

- SEE GROWTH FACTORS (INCL. ANABOLICS), NERVE GROWTH FACTOR

GROWTH FACTORS (INCL. ANABOLICS)

- ** R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)

GROWTH FACTORS (INCL. ANABOLICS), EPIDERMAL GROWTH FACTOR

- ** R23DE-05985-01 Growth factors in salivary secretions

GROWTH FACTORS (INCL. ANABOLICS), NERVE GROWTH FACTOR

- ** R23DE-05985-01 Growth factors in salivary secretions

GROWTH HORMONE-RELEASE INHIBITING FACTOR (GIF)

- SEE PITUITARY-DIENCEPHALON HORMONES, SOMATOSTATIN

GROWTH INHIBITORS

- ** R23DE-05050-02 Sources of toxins from human dental plaque
- R01DE-05640-01 Cytotoxicity of periodontopathic bacteria

GROWTH MEDIA

- R01DE-04903-03 Trace metal uptake in cariogenic streptococcus mutants
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

GROWTH MICROORGANISMS

- SEE ALSO REPRODUCTION MICROORGANISMS
- P50DE-02600-15 0039 Support for oral biology research center - Saliva in abnormal bacterial adherence and colonization (human)
- P01DE-02847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
- P01DE-02847-13 0021 Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)
- R01DE-03118-11 Inhibition of saccharide metabolism by oral flora
- R01DE-03715-06 Cellular assembly--Its role in facial morphogenesis (fungi)
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)
- R01DE-05144-03 Periodontal disease--Role of spirochetes (rabbits, human)
- R01DE-05606-02 Pili of *S. sanguis* and their role in adhesion (human, rabbits)

GROWTH MICROORGANISMS, MICROBIAL CULTURE

- R01DE-01554-20 Host factors in caries resistance (human, rats)
- R01DE-03487-10 Inhibition of human cariogenic streptococci
- R01DE-03488-10 Microbial composition of developing dental plaque
- R01DE-04278-06 Human saliva-streptococcal metabolic interactions
- P50DE-04881-05 0002 Center for clinical research in periodontal diseases - Relationship of subgingival microbiota to the etiology of periodontal diseases
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- R01DE-04957-03 Bacterial metabolites in oral diseases
- R01DE-05104-02 Periodontitis--Microbial etiology and prediction
- R01DE-05144-03 Periodontal disease--Role of spirochetes (rabbits, human)
- R01DE-05606-02 Pili of *S. sanguis* and their role in adhesion (human, rabbits)
- R23DE-05942-01 Airway factors in cleft palate dentofacial deformity
- R23DE-05951-01 Selective microbial ecology of periodontitis siblings

GROWTH REGULATION, CELLULAR

- SEE CELL GROWTH REGULATION

GROWTH RETARDATION INTRAUTERINE

- SEE PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)

GROWTH RETARDATION POSTNATAL

- SEE GROWTH DISORDERS POSTNATAL (SEE ALSO APPROPRIATE SPECIFICS)

GUANIDINES, BIGUANIDES, CHLORHEXIDINE

- R01DE-05334-02 Periodontal therapy by controlled local drug delivery (human)

GUANOSINE MONOPHOSPHATE CYCLIC

- SEE PURINE NUCLEOTIDES, GUANINE NUCLEOTIDES, GMP CYCLIC

GUANYLATE CYCLASE

- SEE NUCLEOTIDYL-CYCLASES, GUANYLATE CYCLASE

GUT LYMPHOID TISSUE DEPENDENT IMMUNITY

- SEE IMMUNITY, HUMORAL IMMUNITY

H ANTIGENS (HISTOCOMPATIBILITY)

- SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

H-2 LOCUS (MOUSE)

- SEE IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)

H-2D ANTIGEN

- SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

H-2G ANTIGENS

- SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

H-2K ANTIGENS

- SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

H2-D GENES

- SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

H2-G GENES

- SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

H2-K GENES

- SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

H2-S GENES

- SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

HALISTERESIS

- SEE SKELETAL DISORDERS, BONE RESORPTION ABNORMAL

HALOALKYLAMINES, CYCLOPHOSPHAMIDE

- R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

HALOGEN POISONING, FLUOROSIS

- SEE ALSO DENTAL DISCOLORATION, DENTAL MOTTLING
- R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

HALOGENS, CHLORINE (COMPOUNDS) SEE ALSO SPECIFICS

- R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
- R23DE-05314-03 Dental alloy corrosion research
- R01DE-05483-02 Characterization of predentinal extracellular fluid (rats)

HALOGENS, FLUORINE (COMPOUNDS) SEE ALSO SPECIFICS

- R01DE-01830-19 Quantitation of enamel demineralization mechanisms
- M P01DE-01850-18 Nutritional sources and metabolic roles of fluoride

- P01DE-01850-18 0068 Nutritional sources and metabolic roles of fluoride - Radioimmunoassay of parathyroid hormone in the rat

- ** P01DE-01850-18 0071 Nutritional sources and metabolic roles of fluoride - Fluoride content of infant, toddler and adult foods

- P01DE-01850-18 0072 Nutritional sources and metabolic roles of fluoride - Effect of fluoride on iron transport (mice)

- ** P01DE-01850-18 0075 Nutritional sources and metabolic roles of fluoride - Metabolic handling of perfluorooctanoic acid (rats)

- ** P01DE-01850-18 0081 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on strain N mice

- P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel

- P50DE-02668-15 0193 Regional dental research center - Metabolism of isolated ameloblasts

- P50DE-02670-15 0020 Institute of Dental Research - Nutrition-Disease proneness during dental development

- P50DE-02731-15 0037 Development support for dental research institute - Luminescence and polarized light in the diagnosis and treatment of caries

- R01DE-03118-11 Inhibition of saccharide metabolism by oral flora

- ** R01DE-04192-07 SnF2-Ca (OH) 2-H3O4-H2O reaction system
- ** R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism

- ** R01DE-04616-04 Fluoride-cadmium interaction in dental caries (rats)

- R01DE-05224-01 Enamel silylation as a caries prevention method (human, animals)

- ** R01DE-05289-03 Fluorine ion binding by early enamel matrix proteins (rats)

- R01DE-05327-03 Polymeric polyphosphonates on dental caries and plaque (rats)

- R01DE-05334-02 Periodontal therapy by controlled local drug delivery (human)

- R01DE-05375-01 Surface composition of biological apatites
- R01DE-05596-02 Typically-applied polymers for caries prevention

- ** R01DE-06113-01 Determinants of fluoride in the oral environment (Dogs, rats)

- ** R01DE-12431-00 Clinical trial of a combined MFP-NaF dentifrice

- R01DE-12434-00 Identify cariogenic elements of food

- ** R01DE-72409-08 Effect of strontium, lithium and fluorine on dental plaque (rats, human)

- R01DE-92422-04 Dental plaque and saliva from gastric intubated patients

HALOGENS, IODINE (COMPOUNDS) SEE ALSO SPECIFICS

- R01DE-05334-02 Periodontal therapy by controlled local drug delivery (human)

HALOHYDROCARBONS, FLUOROXYDROCARBONS (GENERAL)

- SEE ALSO PLASTICS, FLUOROCARBON POLYMERS

- ** P01DE-01850-18 0082 Nutritional sources and metabolic roles of fluoride - Nonionic fluoride in foods (human)

HALOPYRIMIDINE NUCLEOSIDES, HALOURACIL NUCLEOSIDES, 5-BROMODEOXYURIDINE

- ** R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine

HALOPYRIMIDINES, HALOURACIL, FLUOROURACIL

- R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

HANDICAPPED CHILDREN

- SEE CHILDREN, HANDICAPPED CHILDREN

HAPTENS

- SEE IMMUNOLOGY, HAPTENS

HARDNESS, SOLID STATE

- SEE PHYSICAL PROPERTIES, SOLID STATE, HARDNESS

HARE LIP

- SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CLEFT LIP

HAZARDS, OCCUPATIONAL

- SEE OCCUPATIONAL HEALTH, OCCUPATIONAL HAZARDS

HAZARDS OF MEDICAL EQUIPMENT

- SEE BIOMEDICAL ENGINEERING, MEDICAL EQUIPMENT SAFETY

HEAD

- SEE BODY REGIONS, HEAD

HEAD AND NECK NEOPLASMS

- SEE NEOPLASMS OF BODY REGIONS, HEAD AND NECK

HEAD MEASUREMENTS

- SEE BODY PHYSICAL CHARACTERISTICS, CEPHALOMETRY

HEAD MOVEMENT

- SEE SKELETAL MOVEMENT, HEAD MOVEMENT

HEALING

- SEE INJURIES, WOUND HEALING

HEALTH, DISEASE PREVENTION AND CONTROL

- SEE ALSO COMMUNICABLE DISEASE CONTROL

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
 **Oriented significantly to above subject

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

- SEE ALSO DENTISTRY, PREVENTIVE
 SEE ALSO DIAGNOSTIC TESTS, EARLY DIAGNOSIS*
 SEE ALSO EDUCATION, HEALTH EDUCATION
 SEE ALSO EPIDEMIOLOGY AND DISEASE CONTROL STUDY SECTION
 SEE ALSO INJURY (HAZARDS) PREVENTION AND CONTROL, BIOHAZARDS (CONTROL)
 SEE ALSO POPULATION STUDIES HUMAN, EPIDEMIOLOGY
 R01DE-03758-07 Violence characterization and immunization against S mutants (rats, rabbits)
 R01DE-04385-06 Mechanism of dental caries (human)
 ** P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
 R01DE-05414-02 The local immune response in periodontal disease (human)
 R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
 ** R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)
- HEALTH CARE DELIVERY**
 SEE HEALTH CARE SERVICES, PATIENT CARE MANAGEMENT
- HEALTH CARE FACILITIES (SYSTEMS) INFORMATION SYSTEMS**
 SEE BIOMEDICAL SYSTEMS AUTOMATED, HEALTH CARE FACILITIES (SYSTEMS) INFORMATION SYSTEMS
- HEALTH CARE QUALITY**
 ** R01DE-05761-02 Improved dental instruments and materials
 ** R23DE-05858-01 Dentists' behavior and treatment outcomes
- HEALTH CARE SERVICES, CASE FINDING AND OUTREACH**
 R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)
- HEALTH CARE SERVICES, PATIENT CARE MANAGEMENT**
 SEE ALSO HEALTH CARE SERVICES, PATIENT-PROFESSIONAL RELATIONS
 ** R23DE-05799-01 Behavioral methods for pedodontic management (human)
 ** R23DE-05858-01 Dentists' behavior and treatment outcomes
- HEALTH CARE SERVICES, PATIENT-PROFESSIONAL RELATIONS**
 ** R23DE-05799-01 Behavioral methods for pedodontic management (human)
 ** R23DE-05858-01 Dentists' behavior and treatment outcomes
- HEALTH CARE (SERVICES)(RESOURCES) ANALYSIS AND EVALUATION**
 SEE ALSO HEALTH CARE QUALITY
 R01DE-05563-02 The blade implant—Clinical efficacy and safety (human)
- HEALTH CARE (SERVICES)(RESOURCES) UTILIZATION, APPOINTMENTS-VISITS**
 R23DE-05858-01 Dentists' behavior and treatment outcomes
- HEALTH EDUCATION**
 SEE EDUCATION, HEALTH EDUCATION
- HEALTH EDUCATION, DENTAL**
 SEE EDUCATION, HEALTH EDUCATION, DENTAL
- HEALTH INSURANCE, DENTAL**
 R23DE-05497-02 Dental disease and work loss (human)
- HEALTH PROMOTION**
 SEE HEALTH, DISEASE PREVENTION AND CONTROL
- HEALTH RECORD SYSTEMS, PATIENT (DISEASE) REGISTRIES**
 ** P01DE-02872-12 0018 Craniofacial dysmorphology - Date bank—Computerization of clinical data
- HEALTH RECORDS (SYSTEMS) AUTOMATED**
 P01DE-02872-12 0062 Craniofacial dysmorphology - Congenital palatopharyngeal incompetence
- HEALTH SCIENCES PROFESSIONS, ANESTHESIOLOGY**
 ** R13DE-05982-01 Third World Congress on Pain (Scotland)
- HEALTH SCIENCES RESEARCH (GENERAL)***
 SEE ALSO DENTAL RESEARCH*
 R13DE-05468-01 Symposium on orthodontics and bioengineering (Connecticut)
 ** R13DE-05898-01 13th Annual International Biomaterials Symposium - 1981
 R13DE-05982-01 Third World Congress on Pain (Scotland)
- HEARING DISORDERS**
 SEE EAR DISORDERS, HEARING DISORDERS
- HEARING TESTS**
 SEE EAR DISORDERS DIAGNOSIS, HEARING TESTS*
- HEART BYPASS (SHUNT) INTRACARDIAC ABNORMAL**
 SEE CONGENITAL ABNORMALITIES, HEART SEPTAL DEFECTS
- HEART DISORDERS, ENDOCARDITIS BACTERIAL**
 ** R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)
 ** R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)

HEART FUNCTION, HEART RATE

- P01DE-05130-03 0006 Dental/orofacial pain—Mechanisms behavior and modulation - Acute pain in research and clinical settings

HEART RATE

SEE HEART FUNCTION, HEART RATE

HEART SEPTAL DEFECTS

SEE CONGENITAL ABNORMALITIES, HEART SEPTAL DEFECTS

HEAT

SEE TEMPERATURE, HEAT

HEAT STIMULUS

SEE TEMPERATURE, HEAT, CALORIC STIMULATION

HEATING, AIR CONDITIONING, VENTILATION

SEE ENVIRONMENT CONTROLLED

HELA CELLS

SEE NEOPLASTIC CELLS, HELA CELLS

HEMAGGLUTINATION

SEE IMMUNOLOGICAL TESTS AND IMMUNOASSAY, HEMAGGLUTINATION*

HEMAGGLUTININS (PLANT)

SEE PLANTS PROTEINS, LECTINS

HEMATOPOIESIS

SEE BLOOD AND RE SYSTEM, HEMATOPOIESIS

HEMOCYTES

SEE BLOOD CELLS

HEMODYNAMICS

SEE CARDIOVASCULAR FUNCTION, BLOOD CIRCULATION DYNAMICS (GENERAL)

ALPHA HEMOLYTIC GROUP OF STREPTOCOCCI

SEE BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS, VIRIDANS GROUP*

HEMOSTASIS

SEE BLOOD STASIS

HEPARIN

SEE POLYSACCHARIDES, GLYCOSAMINOGLYCANS, HEPARIN

HEPATOTOXINS

SEE LIVER DISORDERS, TOXIC LIVER DISORDERS, HEPATOTOXINS

HERCYNINE

SEE IMIDAZOLES

HEREDITARY DISORDERS

SEE GENETIC DISORDERS (SEE ALSO APPROPRIATE CONGENITAL ABNORMALITIES)

HEREDITARY DISORDERS, METABOLIC ERRORS

SEE METABOLIC DISORDERS INBORN

HEREDITY

SEE GENETICS

HERPES SIMPLEX VIRUS

SEE VIRUSES, HERPESVIRIDAE, ALPHAHERPESVIRINAE

HERPES SIMPLEX VIRUS GROUP

SEE VIRUSES, HERPESVIRIDAE, ALPHAHERPESVIRINAE

HERPESVIRUS HOMINIS

SEE VIRUSES, HERPESVIRIDAE, ALPHAHERPESVIRINAE

HERPESVIRUS INFECTIONS

SEE VIRUS DISEASES, HERPESVIRIDAE

HETEROGENETIC ANTIGENS

SEE IMMUNOLOGY, ANTIGENS, HETERODGENETIC ANTIGENS

HETEROLOGOUS TRANSPLANTATION

SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION HETEROLOGOUS

HETEROTRANSPLANTATION

SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION HETERODLOGOUS

HETEROZYGOTES

SEE GENETICS, GENOTYPES, HETEROZYGOTES

HEURISTICS (ARTIFICIAL INTELLIGENCE)

SEE COMPUTER, ARTIFICIAL INTELLIGENCE, PATTERN RECOGNITION AND CONTROL SYSTEMS

HEXOSANS, GLUCANS

- P50DE-02731-15 0019 Development support for dental research institute - Structure and maintenance of extrachromosomal DNA in streptococci
 R01DE-03258-10 Streptococcus mutants—Dental caries mechanism (human)
 R01DE-03758-07 Violence characterization and immunization against S mutants (rats, rabbits)
 R01DE-04061-07 Salivary antibodies to S mutants—Induction and effects (monkeys)
 R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
 R01DE-05102-04 Potential anti-carries agents (rats)
 R01DE-05141-03 Cariogenic mechanisms of gingival plaque bacteria
 R01DE-05427-01 Adherence mechanisms of oral microbes

HEXOSANS, GLUCANS, DEXTRAN

- P50DE-02731-15 0019 Development support for dental research institute - Structure and maintenance of extrachromosomal DNA in streptococci
 ** R01DE-03118-11 Inhibition of saccharide metabolism by oral flora
 ** R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)
 ** R01DE-03578-10 polysaccharides Biosynthetic study of dental plaque
 R01DE-03654-09 Molecular basis of dental caries (human)
 ** R01DE-03731-06 Dextran sucrose of Streptococcus sanguis
 R01DE-03739-09 Glycosyltransferases from oral bacteria (bacteria)

HEXOSANS, GLUCANS, DEXTRINS

- ** R01DE-03578-10 Biosynthetic study of dental plaque polysaccharides

HEXOSANS, GLUCANS, STARCH

SEE ALSO HEXOSANS, GLUCANS, DEXTRINS
 N01DE-12434-00 Identify cariogenic elements of food

HEXOSANS, LEVANS

- R01DE-03578-10 Biosynthetic study of dental plaque polysaccharides
 R01DE-05141-03 Cariogenic mechanisms of gingival plaque bacteria

HEXOSES

- P50DE-02600-15 0040 Support for oral biology research center - Fate of actinomyces viscosus components within phagocytic cells

HEXOSES, DEOXYHEXOSES

- R01DE-05017-03 Characterization of surface antigens of S mutants

HEXOSES, FRUCTOSE

- N01DE-02427-04 Synthesize noncariogenic sweeteners
 R01DE-03739-09 Glycosyltransferases from oral bacteria (bacteria)

HEXOSES, GLUCOSE

- SEE ALSO CARBOHYDRATES METABOLISM, GLUCOSE METABOLISM
 SEE ALSO CARBOHYDRATES TRANSPORT, GLUCOSE TRANSPORT
 SEE ALSO HEXOSES, GLYCOLYSIS
 R01DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)
 R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
 R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)
 R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
- HEXOSES, GLYCOLYSIS**
 SEE ALSO TRICARBOXYLIC ACIDS, KREBS CYCLE
 R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism
 R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
 R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
 R23DE-05809-01 Effects of fluoride on physiology of oral bacteria

HG

SEE METALS, HEAVY METALS, MERCURY (COMPOUNDS)

HH ANTIGENS

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

HH GENE

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

HIGH RISK, DISEASE PRONENESS

SEE DISEASE PRONENESS-RISK

HIGH-RISK PREGNANCIES (INTRAUTERINE FAILURE TO THRIVE)

SEE PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)

HIRSCHSPRUNG'S DISEASE

SEE CONGENITAL ABNORMALITIES, GASTROINTESTINAL, MEGACOLON CONGENITAL

HISTAMINE

SEE IMIDAZOLES, HISTAMINE

HISTAMINE LIBERATION

SEE IMIDAZOLES, HISTAMINE LIBERATION

HISTIDINE

SEE CYCLIC AMINO ACIDS, HISTIDINE

HISTOCHEMISTRY AND CYTOCHEMISTRY (GENERAL)*

- ** P50DE-02668-15 0196 Regional dental research center - Cytochemical demonstration of macromolecules of craniofacial tissue
 R01DE-03934-07 Differentiation of oral epithelium (rats)
 R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)

(contd.)

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 **Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

- R01DE-04857-02** Temporalis flaps in the treatment of facial paralysis (monkeys)
R23DE-05232-03 Growth and function of the muscles of mastication (monkeys)
R01DE-05323-02 Calcium transport in developing dental tissues (frogs, rats)
R23DE-05424-03 Quantitative studies of lysosomes in amelogenesis (rats)
R01DE-05550-01 Cell death during craniofacial embryogenesis
R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
- HISTOCOMPATIBILITY**
 SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOIMMUNITY
- HISTOCOMPATIBILITY ANTIGENS**
 SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)
- HISTOCOMPATIBILITY GENES**
 SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES
- HISTOGENESIS**
 SEE GROWTH AND DEVELOPMENT, HISTOGENESIS
- HISTOLOGY (GENERAL)***
R01DE-04857-02 Temporalis flaps in the treatment of facial paralysis (monkeys)
 ** **R01DE-05078-05** Craniofacial growth and remodeling (human)
R01DE-05190-03 Factors determining variation in adult oral mucosa
R01DE-05292-03 Biological prosthetic attachment (dog)
R01DE-05769-03 Ultrastructure of tooth development
- HISTOPATHOLOGY (GENERAL)***
R01DE-02525-16 Ultrastructural histopathology of human dental enamel
R01DE-03301-11 Connective tissue of the periodontium--Collagen maturation
R01DE-04808-02 Virulence factors of gram negative corroding bacteria
R01DE-05679-01 Pathophysiology of MPD and other facial pain syndromes (animals)
- HLA-A3 ANTIGEN**
 SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)
- HLA-B7 ANTIGEN**
 SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)
- HLA-B27 ANTIGEN**
 SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)
- HLA-D ANTIGEN**
 SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)
- HLA-DW2 ANTIGEN**
 SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)
- HL-A LOCUS (HUMAN)**
 SEE IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)
- HOLOGRAPHY**
 SEE OPTICS, PHOTOGRAPHY, HOLOGRAPHY*
- HOM-1 GENE**
 SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES
- HOMEOSTASIS, HOMEOSTATIC CONTROL**
 SEE INFORMATION PROCESSING AND CONTROL (BIOLOGICAL), HOMEOSTASIS
- HOMOLOGOUS TRANSPLANTATION**
 SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION HOMOLOGOUS
- HOMOTRANSPLANTATION**
 SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION HOMOLOGOUS
- HORMONAL REGULATION AND CONTROL (MECHANISMS)**
 SEE ENDOCRINOLOGY, HORMONAL REGULATION AND CONTROL (MECHANISMS)
- HORMONE BINDING PROTEINS**
 SEE ENDOCRINOLOGY, HORMONE BINDING PROTEINS
- HORMONE RECEPTORS**
 SEE ENDOCRINOLOGY, HORMONE RECEPTORS
- HORMONES BIOSYNTHESIS**
 SEE ENDOCRINOLOGY, HORMONES BIOSYNTHESIS
- HOSPITAL INFORMATION SYSTEMS**
 SEE BIOMEDICAL SYSTEMS AUTOMATED, HEALTH CARE FACILITIES (SYSTEMS) INFORMATION SYSTEMS
- HOST-MICROORGANISM**
 SEE ENVIRONMENT, ECOLOGY ORGANISMS, HOST-ORGANISM
- HOST-ORGANISM**
 SEE ENVIRONMENT, ECOLOGY ORGANISMS, HOST-ORGANISM
- HOST-VIRUS**
 SEE VIRUS DISEASE CHARACTERISTICS, HOST-VIRUS

HR GENE

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

HUMAN AND HUMAN RELATED POPULATION STUDIES

SEE POPULATION STUDIES HUMAN

HUMAN EMBRYOLOGY AND DEVELOPMENT STUDY SECTION

SEE EMBRYOLOGY (HUMAN) AND DEVELOPMENT STUDY SECTION

HUMORAL ANTIBODIES (GENERAL)

SEE IMMUNOLOGY, ANTIBODIES

HUMORAL (ANTIBODY) HYPERSENSITIVITY

SEE HYPERSENSITIVITY, IMMEDIATE HYPERSENSITIVITY

HUMORAL IMMUNITY

SEE IMMUNITY, HUMORAL IMMUNITY

HURLER'S SYNDROME

SEE METABOLIC DISORDERS INBORN, MUCOPOLYSACCHARIDOSIS, LIPOCHONORODYSTROPHY

HYALURONIC ACID

SEE POLYSACCHARIDES, GLYCOSAMINOGLYCANS, HYALURONIC ACID

HYALURONIDASE

SEE CARBOHYDRASES, HYALURONIDASE

HYALURONOGUCOSIDASE

SEE CARBOHYDRASES, HYALURONIDASE

HYBRID CELLS

SEE CELL HYBRIDS

HYBRIDOMAS

SEE CELL HYBRIDS, HYBRIDOMAS

HYBRIDS

SEE GENETICS, GENOTYPES, HETEROZYGOTES

HYDRATION-DEHYDRATION

SEE CHEMICAL REACTIONS, HYDRATION-DEHYDRATION

HYDRATION REACTIONS

SEE CHEMICAL REACTIONS, HYDRATION-DEHYDRATION

HYDROCORTISONE

SEE ADRENAL CORTEX HORMONES, HYDROCORTISONE

HYDROGEN-ION CONCENTRATION

SEE ACIDS-BASES, HYDROGEN-ION CONCENTRATION

HYDROLASES

SEE ALSO CARBOHYDRASES

SEE ALSO PHOSPHATASES

P50DE-02623-14 0023 Center for oral health research -

Interactions of oral bacteria and polymorphonuclear leukocytes

R01DE-03995-07 Leukocytes in the pathogenesis of

periodontal disease (human, mice)

R01DE-05640-01 Cytotoxicity of periodontopathic bacteria

HYDROLYSIS

SEE CHEMICAL REACTIONS, SOLVOLYSIS, HYDROLYSIS

HYDROPHOBIC BONDS

SEE CHEMICAL BONDS, HYDROPHOBIC

HYDROPS

SEE BODY FLUID BALANCE, EDEMA

HYDROXYAPATITE

SEE CALCIUM PHOSPHATES, HYDROXYAPATITE

2-HYDROXYBENZOIC ACID

SEE PHENYLCARBOXYLATES, SALICYLATES

25-HYDROXYCHOLECALCIFEROL

SEE VITAMIN D GROUP, VITAMIN D3, 25-HYDROXY-

HYDROXYDAUNOMYCIN

SEE ANTIBIOTICS, ANTHRACYCLINES, ADRIAMYCIN

HYDROXYLASES (GENERAL)

SEE OXYGENASES, HYDROXYLASES (GENERAL)

HYDROXYL GROUPS

R01DE-01912-18 Tooth enamel apatite at the atomic level (human)

P50DE-02670-15 0003

Institute of Dental Research -

Biochemistry of collagenous and noncollagenous proteins of

connective tissues

R23DE-05155-02 Active principles of dental pulp therapeutic

agents

HYDROXYPROLINE

SEE CYCLIC AMINO ACIDS, PROLINE, HYDROXYPROLINE

HYDROXYPROPIONIC ACID

SEE FATTY ACIDS, LACTATES

5-HYDROXYTRYPTAMINE

SEE BENZOPYRROLES, SEROTONIN

HYPERALIMENTATION (THERAPY)

SEE NUTRITION, DIET THERAPEUTIC, HYPERALIMENTATION (THERAPY)

HYPERKERATOSIS, SKIN

SEE SKIN DISORDERS, SKIN KERATOSIS

HYPERPARATHYROIDISM

SEE PARATHYROID GLANDS DISORDERS, HYPERPARATHYROIDISM

HYPERSENSITIVITY (GENERAL)SEE ALSO ALLERGY AND IMMUNOLOGY STUDY SECTION
 SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT, IMPLANT COMPATIBILITY

P50DE-02623-14 0031 Center for oral health research - Role of immunity in periodontal disease (rats)

HYPERSENSITIVITY, ANAPHYLAXIS, ARTHUS PHENOMENON

R01DE-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)

HYPERSENSITIVITY, DELAYED**HYPERSENSITIVITY**

SEE ALSO HYPERSENSITIVITY, LYMPHOKINES

SEE ALSO HYPERSENSITIVITY, LYMPHOKINES, LEUKOTAXIC

FACTOR

SEE ALSO HYPERSENSITIVITY, LYMPHOKINES, LYMPHOTOXIN

SEE ALSO HYPERSENSITIVITY, LYMPHOKINES, MIGRATION

INHIBITORY FACTOR

SEE ALSO IMMUNITY, CELLULAR IMMUNITY (GENERAL)

SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT,

ISOALLOIMMUNITY

** R01DE-03408-09 Immunopathology of gingivitis and

periodontitis (monkeys, human)

R01DE-04501-06 Cell mediated immunity in gingival

inflammation (mice)

HYPERSENSITIVITY, IMMEDIATE**HYPERSENSITIVITY**

SEE ALSO IMMUNOLOGY, ANTIGEN-ANTIBODY REACTIONS, IMMUNE COMPLEXES

** R01DE-03408-09 Immunopathology of gingivitis and

periodontitis (monkeys, human)

HYPERSENSITIVITY, LYMPHOKINES

P50DE-02623-14 0033 Center for oral health research -

Immune system in regulation of angiogenesis

** R01DE-04808-02 Virulence factors of gram negative corroding

bacteria

P50DE-04898-05 0001 Periodontal disease research center -

Microbiology (human)

R01DE-05413-02 Bone resorption in periodontal disease

R01DE-05467-02 Pathogenesis of localized bone destruction

R01DE-05505-02 Periodontitis and host defense in juvenile

diabetes (human)

R01DE-05626-01 Role of complement in periodontal disease

HYPERSENSITIVITY, LYMPHOKINES,**LEUKOTAXIC FACTOR**

R01DE-04808-02 Virulence factors of gram negative corroding

bacteria

** R01DE-05640-01 Cytotoxicity of periodontopathic bacteria

HYPERSENSITIVITY, LYMPHOKINES,**LYMPHOCYTE TRANSFORMING FACTORS**

R01DE-05505-02 Periodontitis and host defense in juvenile

diabetes (human)

HYPERSENSITIVITY, LYMPHOKINES,**LYMPHOTOXIN**

R23DE-05240-03 Immunological studies--Caries and

periodontal disease (mice)

HYPERSENSITIVITY, LYMPHOKINES,**MIGRATION INHIBITORY FACTOR**

R01DE-04808-02 Virulence factors of gram negative corroding

bacteria

R01DE-05505-02 Periodontitis and host defense in juvenile

diabetes (human)

HYPERSENSITIVITY, LYMPHOKINES,**OSTEOCLAST ACTIVATING FACTOR**

P50DE-04881-05 0004 Center for clinical research in

periodontal diseases - Relation of inflammation mediators to

destructive periodontal diseases

** R01DE-05467-02 Pathogenesis of localized bone destruction

R01DE-05505-02 Periodontitis and host defense in juvenile

diabetes (human)

HYPERSENSITIVITY, RESPIRATORY**HYPERSENSITIVITY, ASTHMA**

R01DE-01554-20 Host factors in caries resistance (human,

rats)

HYPERSENSITIVITY TESTS

R01DE-03408-09 Immunopathology of gingivitis and

periodontitis (monkeys, human)

HYPERVITAMINOSIS

SEE NUTRITIONAL ABNORMALITIES, HYPERVITAMINOSIS

HYPNOTICS AND SEDATIVES

SEE PSYCHOPHARMACOLOGICAL AGENTS, HYPNOTICS AND

SEDATIVES

HYPOIMMUNITY

SEE IMMUNITY, IMMUNOLOGICAL UNRESPONSIVENESS

HYPOPHOSPHATEMIA, FAMILIAL

SEE METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT

RICKETS INBORN

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

(contd).

HYPOTENSIVE PEPTIDES

SEE PEPTIDES, VASOACTIVE PEPTIDES, HYPOTENSIVE PEPTIDES

HYPOVITAMINOSIS A

SEE NUTRITIONAL ABNORMALITIES, HYPOVITAMINOSIS A

HYPOVITAMINOSIS D

SEE NUTRITIONAL ABNORMALITIES, HYPOVITAMINOSIS D

I

SEE HALOGENS, IODINE (CDMPOUNDS) SEE ALSO SPECIFICS

IA ANTIGENS

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALDANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

IDIOTYPES

SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL

IDUONIDASE DEFICIENCY DISEASE (HURLER'S SYNDROME)

SEE METABOLIC DISORDERS INBORN, MUCOPOLYSACCHARIDOSIS, LIPOCHONDRODYSTROPHY

IG GENES

SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL

IGA SECRETORY

SEE IMMUNOLOGY, SECRETORY (ANTIBODY) (FACTOR) SYSTEM

ILIUM

SEE SKELETAL SYSTEM, PELVIC BONES, ILIUM

IMAGE AND WAVESHAPE PROCESSING ANALYSIS AND DISPLAY

SEE OPTICS, IMAGE PROCESSING ANALYSIS AND DISPLAY*

IMIDAZOLEIDONES, HYDANTOINS, DIPHENYLHYDANTOIN

P50DE-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)

R01DE-04039-04 Sex steroid metabolism in oral tissues

R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)

** R01DE-05041-03 Orofacial anomalies in phenytoin teratogenesis (mice, human)

R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)

** R01DE-05459-02 Phenytoin-Pathogenesis of gingival overgrowth (cats)

IMIDAZOLES

SEE ALSO ALKALOIDS, PILOCARPINE TYPE

SEE ALSO CYCLIC AMINO ACIDS, HISTIDINE

R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)

IMIDAZOLES, HISTAMINE

R23DE-05605-01 The humoral regulation of pulp circulation (rats)

IMIDAZOLES, HISTAMINE LIBERATION

R01DE-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)

IMIDAZOLES, METRONIDAZOLE

R01DE-05334-02 Periodontal therapy by controlled local drug delivery (human)

IMINES, SCHIFF BASES

P50DE-02668-15 0125 Regional dental research center - Collagen crosslinks and the fate of extracellular matrix

8,9C-**IMINOETHANOPHENANTHRO(4,5BCD)FURANS**

SEE ALKALOIDS, MORPHINES

IMITATION FOODS

SEE FOOD SCIENCES AND TECHNOLOGY, SYNTHETIC FOODS

IMMEDIATE HYPERSENSITIVITY

SEE HYPERSENSITIVITY, IMMEDIATE HYPERSENSITIVITY

IMMUNE COMPLEXES

SEE IMMUNOLOGY, ANTIGEN-ANTIBODY REACTIONS, IMMUNE COMPLEXES

IMMUNE DISORDERS

SEE IMMUNOPATHOLOGY (GENERAL)

IMMUNE SERA

SEE IMMUNOLOGY, ANTIBODIES, IMMUNE SERA

IMMUNE TOLERANCE

SEE IMMUNITY, IMMUNOLOGICAL UNRESPONSIVENESS

IMMUNITY (AND NATURAL RESISTANCE) (GENERAL)

SEE ALSO IMMUNOLOGY, ANTIBODIES, IMMUNE SERA

SEE ALSO IMMUNOLOGY, ANTIBODY FORMATION

SEE ALSO IMMUNOLOGY, ANTIGEN-ANTIBODY REACTIONS

** P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)

IMMUNITY, BACTERICIDAL DEFENSES (GENERAL)

SEE ALSO IMMUNOLOGY, ANTIBODIES, OPSONINS

SEE ALSO IMMUNOLOGY, ANTIBODIES BACTERIAL

SEE ALSO VACCINES, BACTERIAL (GENERAL)

** P50DE-02623-14 0031 Center for oral health research - Role of immunity in periodontal disease (rats)

R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)

** R01DE-04217-07 Effective immunity to dental caries--Cellular basis

** R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)

R01DE-04278-06 Human saliva-streptococcal metabolic

interactions

** P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)

R01DE-05706-01 Role of microbial collagenases in periodontal disease

R01DE-05723-01 Spirochete influence on immunity in oral disease

R01DE-05747-01 Monoclonal antibody analysis of S. mutans antigens

IMMUNITY, CELLULAR IMMUNITY (GENERAL)

SEE ALSO BLOOD CELLS, LYMPHOCYTES, KILLER CELLS

SEE ALSO BLOOD CELLS, T LYMPHOCYTES

SEE ALSO HYPERSENSITIVITY, DELAYED HYPERSENSITIVITY

SEE ALSO HYPERSENSITIVITY, LYMPHOKINES

SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOIMMUNITY

P50DE-02623-14 0031 Center for oral health research - Role of immunity in periodontal disease (rats)

** P50DE-02670-15 0037 Institute of Dental Research -

** R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)

** R01DE-04217-07 Effective immunity to dental caries--Cellular basis

** R01DE-04501-06 Cell mediated immunity in gingival inflammation (mice)

P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)

P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations

R01DE-05330-02 Herpes virus antibodies in patients with oral cancer

R23DE-05331-01 Local host mechanism in periodontal disease (human, monkeys)

** R01DE-05414-02 The local immune response in periodontal disease (human)

R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

R01DE-05626-01 Role of complement in periodontal disease

R01DE-05723-01 Spirochete influence on immunity in oral disease

R01DE-05729-01 Etiological mechanisms in periodontal disease

** R01DE-05732-02 Specificity of cell mediated immune response in periodontal disease

R23DE-05789-01 IgA receptor bearing oral cells in cystic fibrosis (human)

IMMUNITY, CELLULAR, LYMPHOCYTE ACTIVATION, TRANSFORMATION AND PROLIFERATION

SEE ALSO HYPERSENSITIVITY, LYMPHOKINES, LYMPHOCYTE

TRANSFORMING FACTORS

R01DE-03408-09 Immunopathology of gingivitis and

periodontitis (monkeys, human)

R01DE-03420-09 Immune phenomena in experimental

periodontal disease (rats)

R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)

R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)

P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)

R01DE-05089-03 Oral herpes simplex--An approach to dental therapy (hamsters)

R01DE-05414-02 The local immune response in periodontal disease (human)

R01DE-05723-01 Spirochete influence on immunity in oral disease

IMMUNITY, CROSS IMMUNITY

SEE ALSO MICROBIAL IDENTIFICATION AND CLASSIFICATION, SEROTYPING

R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)

R01DE-05696-01 Streptococcus mutans interaction with animal tissue (also human)

** R01DE-72408-06 Cross-reacting antigens/oral flora acidogenic bacteria

IMMUNITY, HUMORAL IMMUNITY

SEE ALSO BLOOD CELLS, B LYMPHOCYTES

SEE ALSO GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN (S)

SEE ALSO IMMUNOLOGY, COMPLEMENT

P50DE-02623-14 0031 Center for oral health research - Role of immunity in periodontal disease (rats)

** R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)

P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)

P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations

R23DE-05331-01 Local host mechanism in periodontal disease (human, monkeys)

R01DE-05414-02 The local immune response in periodontal disease (human)

R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

** R23DE-05605-01 The humoral regulation of pulp circulation (rats)

R01DE-05626-01 Role of complement in periodontal disease

R01DE-05729-01 Etiological mechanisms in periodontal disease

IMMUNITY, IMMUNIZATION**(IMMUNOTHERAPY)**

R01DE-05017-03 Characterization of surface antigens of S mutants

** R01DE-04234-21 Anti-carries immunization in sub-human primates

IMMUNITY, IMMUNIZATION ACTIVE

** R01DE-03758-07 Virulence characterization and immunization against S mutans (rats, rabbits)

R01DE-05180-03 Composition of S mutans in different growth environments

R01DE-05696-01 Streptococcus mutans interaction with animal tissue (also human)

IMMUNITY, IMMUNIZATION PASSIVE

R01DE-05696-01 Streptococcus mutans interaction with animal tissue (also human)

IMMUNITY, IMMUNOLOGICAL**UNRESPONSIVENESS**

SEE ALSO IMMUNITY, IMMUNOSUPPRESSION

SEE ALSO IMMUNOPATHOLOGY, IMMUNOLOGIC DEFICIENCY DISORDERS

SEE ALSO METABOLIC DISORDERS INBORN, CHEDIAK-HIGASHI SYNDROME

SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT, GRAFT VERSUS HOST REACTIONS

R01DE-04278-06 Human saliva-streptococcal metabolic interactions

IMMUNITY, IMMUNOREGULATION

SEE ALSO IMMUNITY, IMMUNOSUPPRESSION

SEE ALSO IMMUNOGENETICS (GENERAL)

SEE ALSO IMMUNOLOGY, TOXIC REACTIONS AND MECHANISMS IN IMMUNOLOGY

R01DE-01554-20 Host factors in caries resistance (human, rats)

P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)

P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction

P50DE-02623-14 0031 Center for oral health research - Role of immunity in periodontal disease (rats)

P50DE-02623-14 0032 Center for oral health research - Interactions of salivary agglutinins and oral bacteria

P50DE-02670-15 0037 Institute of Dental Research -

** P50DE-02731-15 0035 Development support for dental research institute - Immune regulation in periodontal disease

R01DE-03420-09 Immune phenomena in experimental periodontal disease (rats)

R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)

R01DE-04217-07 Effective immunity to dental caries--Cellular basis

R01DE-04489-06 Tooth transplantation genetics and immunology (mice, monkeys)

P50DE-04881-05 0003 Center for clinical research in periodontal diseases - Host immunologic response to oral microorganisms

P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)

R23DE-05117-03 Enhancement of oral cancer after allografting (mice)

P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations

P50DE-05139-04 0003 Clinical research center for periodontal disease

R01DE-05330-02 Herpes virus antibodies in patients with oral cancer

** R01DE-05359-01 Regulation of secretory immunity to S mutans (mice)

R01DE-05414-02 The local immune response in periodontal disease (human)

** R23DE-05605-01 The humoral regulation of pulp circulation (rats)

R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

R01DE-05732-02 Specificity of cell mediated immune response in periodontal disease

IMMUNITY, IMMUNOSUPPRESSION

P50DE-02623-14 0031 Center for oral health research - Role of immunity in periodontal disease (rats)

IMMUNITY, IMMUNOSUPPRESSION, ALLOANTISERA

R01DE-04489-06 Tooth transplantation genetics and immunology (mice, monkeys)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

(contd).

- R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)
- IMMUNITY, IMMUNOSUPPRESSIVE AGENTS**
R01DE-05089-03 Oral herpes simplex--An approach to dental therapy (hamsters)
- IMMUNITY, ISOIMMUNITY**
SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOIMMUNITY
- IMMUNIZATION**
SEE IMMUNITY, IMMUNIZATION (IMMUNOTHERAPY)
- IMMUNIZATION ACTIVE**
SEE IMMUNITY, IMMUNIZATION ACTIVE
- IMMUNIZATION PASSIVE**
SEE IMMUNITY, IMMUNIZATION PASSIVE
- IMMUNOASSAY**
SEE IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOASSAY*
- IMMUNOBIOLOGY STUDY SECTION**
** R23DE-05117-03 Enhancement of oral cancer after allografting (mice)
- IMMUNOCHEMISTRY**
R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)
R01DE-03487-10 Inhibition of human cariogenic streptococci
R01DE-03934-07 Differentiation of oral epithelium (rats)
R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)
R01DE-04971-03 Human salivary antigens--Characterization (monkeys)
R01DE-05156-03 Immunoidentification of periodontal plaque bacteria
R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)
** R01DE-05352-03 Immunochemical studies in periodontal disease
R01DE-05467-02 Pathogenesis of localized bone destruction
R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)
R01DE-05531-03 Salivary immune factors (human, bacteria)
R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
N01DE-42434-21 Anti-caries immunization in sub-human primates
- IMMUNODIAGNOSIS (GENERAL)**
SEE IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOLOGICAL TESTS*
- IMMUNODIAGNOSIS OF NEOPLASMS**
SEE NEOPLASMS DIAGNOSIS, IMMUNODIAGNOSIS OF NEOPLASMS
- IMMUNODIFFUSION TEST**
SEE IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNODIFFUSION TESTS*
- IMMUNOFLOURESCENCE**
SEE IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOFLOURESCENCE*
- IMMUNOGENETICS (GENERAL)**
SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOIMMUNITY
** P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
P01DE-02848-11 0002 Biology of connective tissue, bones, and teeth - Steroid receptors in craniofacial teratology (mice)
P01DE-02848-11 0003 Biology of connective tissue, bones, and teeth - Mandibular morphogenesis--Embryonic neonatal and postnatal development (mice)
** R01DE-04489-06 Tooth transplantation genetics and immunology (mice, monkeys)
R01DE-04808-02 Virulence factors of gram negative corroding bacteria
R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)
R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)
** R13DE-05897-01 Oral immunogenetics and tissue transplantation (symposium)
- IMMUNOGENETICS, HISTOCOMPATIBILITY GENES**
** R01DE-05041-03 Orofacial anomalies in phenytoin teratogenesis (mice, human)
R23DE-05117-03 Enhancement of oral cancer after allografting (mice)
- IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL**
** P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
- IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)**
SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)
R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)
** R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)
- ** R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)
** R01DE-05322-01 Genetic analysis of birth defects involving septa (human, mice)
** R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)
- IMMUNOGLOBULIN A**
SEE GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN A
- IMMUNOGLOBULIN A, SECRETORY**
SEE IMMUNOLOGY, SECRETORY (ANTIBODY) (FACTOR) SYSTEM
- IMMUNOGLOBULIN BIOSYNTHESIS**
SEE GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN BIOSYNTHESIS
- IMMUNOGLOBULIN D**
SEE GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN D
- IMMUNOGLOBULIN E**
SEE GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN E
- IMMUNOGLOBULIN G**
SEE GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN G
- IMMUNOGLOBULIN M**
SEE GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN M
- IMMUNOGLOBULIN RECEPTORS**
SEE IMMUNOLOGY, ANTIBODIES, ANTIBODY RECEPTORS
- IMMUNOGLOBULINS**
SEE GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN(S)
- IMMUNOLOGIC DEFICIENCY DISORDERS**
SEE IMMUNOPATHOLOGY, IMMUNOLOGIC DEFICIENCY DISORDERS
- IMMUNOLOGIC REACTIVITY CONTROL**
SEE IMMUNITY, IMMUNOREGULATION
- IMMUNOLOGICAL PARALYSIS**
SEE IMMUNITY, IMMUNOLOGICAL UNRESPONSIVENESS
- IMMUNOLOGICAL SCIENCES STUDY SECTION**
** R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)
- IMMUNOLOGICAL TESTS**
SEE IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOLOGICAL TESTS*
- IMMUNOLOGICAL TESTS AND IMMUNOASSAY, AGGLUTINATION REACTION (AGGLUTININ)***
SEE ALSO CELL ADHESION
SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, HEMAGGLUTINATION*
P50DE-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins
R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence
R01DE-05773-01 Ligand receptor interactions of cariogenic bacteria
N01DE-62491-12 Use of mutants of cariogenic streptococci to prevent dental caries (rats)
- IMMUNOLOGICAL TESTS AND IMMUNOASSAY, HEMAGGLUTINATION***
R01DE-05640-01 Cytotoxicity of periodontopathic bacteria
- IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOASSAY***
SEE ALSO BIOASSAY*
R01DE-05467-02 Pathogenesis of localized bone destruction
- IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNODIFFUSION TESTS***
R01DE-05156-03 Immunoidentification of periodontal plaque bacteria
- IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOFLOURESCENCE***
P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
- IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOLOGICAL TESTS***
SEE ALSO HYPERSENSITIVITY TESTS
SEE ALSO NEOPLASMS DIAGNOSIS, IMMUNODIAGNOSIS OF NEOPLASMS
P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations
P50DE-05139-04 0003 Clinical research center for periodontal disease
- IMMUNOLOGICAL TESTS AND IMMUNOASSAY, RADIOIMMUNOASSAY***
** P01DE-01850-18 0068 Nutritional sources and metabolic roles of fluoride - Radioimmunoassay of parathyroid hormone in the rat
- IMMUNOLOGICAL UNRESPONSIVENESS**
SEE IMMUNITY, IMMUNOLOGICAL UNRESPONSIVENESS
- IMMUNOLOGY, ANTIBODIES**
SEE ALSO GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN(S)
- ** P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction
P01DE-02847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
R01DE-04296-07 Lysozyme--Cell surface interactions and oral defense
- IMMUNOLOGY, ANTIBODIES, AGGLUTININS**
SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, AGGLUTINATION REACTION (AGGLUTININ)*
** P50DE-02623-14 0032 Center for oral health research - Interactions of salivary agglutinins and oral bacteria
- IMMUNOLOGY, ANTIBODIES, ANTIBODY RECEPTORS**
R01DE-05414-02 The local immune response in periodontal disease (human)
** R23DE-05789-01 IgA receptor bearing oral cells in cystic fibrosis (human)
- IMMUNOLOGY, ANTIBODIES, IMMUNE SERA**
SEE ALSO MICROBIAL IDENTIFICATION AND CLASSIFICATION, SEROTYPING
R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)
** N01DE-72408-06 Cross-reacting antigens/oral flora acidogenic bacteria
- IMMUNOLOGY, ANTIBODIES, OPSONINS**
SEE ALSO IMMUNOLOGY, COMPLEMENT
P50DE-05139-04 0003 Clinical research center for periodontal disease
- IMMUNOLOGY, ANTIBODIES BACTERIAL**
P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction
** R01DE-04061-07 Salivary antibodies to S mutans--Induction and effects (monkeys)
** P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)
R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- IMMUNOLOGY, ANTIBODIES VIRAL**
P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction
** R01DE-05330-02 Herpes virus antibodies in patients with oral cancer
- IMMUNOLOGY, ANTIBODY FORMATION**
SEE ALSO GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN BIOSYNTHESIS
R01DE-03934-07 Differentiation of oral epithelium (rats)
R01DE-04061-07 Salivary antibodies to S mutans--Induction and effects (monkeys)
R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)
R01DE-05414-02 The local immune response in periodontal disease (human)
** R01DE-05723-01 Spirochete influence on immunity in oral disease
- IMMUNOLOGY, ANTIGEN-ANTIBODY REACTIONS**
SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, AGGLUTINATION REACTION (AGGLUTININ)*
SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, HEMAGGLUTINATION*
SEE ALSO IMMUNOLOGY, ANTIBODIES, ANTIBODY RECEPTORS
SEE ALSO IMMUNOLOGY, SEROLOGY*
P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
R01DE-04061-07 Salivary antibodies to S mutans--Induction and effects (monkeys)
** R01DE-04217-07 Effective immunity to dental caries--Cellular basis
R01DE-04296-07 Lysozyme--Cell surface interactions and oral defense
R01DE-04645-04 A genetic-biochemical analysis of spirochete motility
R01DE-05427-01 Adherence mechanisms of oral microbes
- IMMUNOLOGY, ANTIGEN-ANTIBODY REACTIONS, IMMUNE COMPLEXES**
SEE ALSO HYPERSENSITIVITY, ANAPHYLAXIS, ARTHUS PHENOMENON
R01DE-05512-02 Role of macrophages in periodontal disease
- IMMUNOLOGY, ANTIGENS**
SEE ALSO IMMUNOLOGY, HAPTENS
SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)
SEE ALSO TOXINS
** R01DE-04971-03 Human salivary antigens--Characterization (monkeys)
- IMMUNOLOGY, ANTIGENS, HETEROGENETIC ANTIGENS**
SEE ALSO IMMUNOLOGY, HAPTENS
R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

(contd).

IMMUNOLOGY, ANTIGENS, SURFACE ANTIGENS (GENERAL)

SEE ALSO IMMUNOLOGY, ANTIGENS MICROBIAL
SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT,
ISOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

- P50DE-02600-15 0035 Support for oral biology research center - Serotyping of microbes for diagnosis of periodontitis (rabbits)
- P50DE-02623-14 0005 Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- ** P50DE-02623-14 0014 Center for oral health research - Surface receptors on plaque forming organisms
- P50DE-02670-15 0025 Institute of Dental Research - Biochemical basis for the cariogenic property of *Streptococcus mutans* (rat)
- R01DE-03180-11 Microbiologic studies of the human oral streptococci
- R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)
- R01DE-04174-07 Variations in the surface structures of oral bacteria
- R01DE-04175-07 Variations in the surface structures of oral bacteria
- R01DE-04217-07 Effective immunity to dental caries--Cellular basis
- R01DE-04529-05 Replacement therapy of dental caries (rats, monkeys)
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- ** R01DE-05017-03 Characterization of surface antigens of *S. mutans*
- R01DE-05180-03 Composition of *S. mutans* in different growth environments
- R01DE-05352-03 Immunochemical studies in periodontal disease
- R01DE-05696-01 *Streptococcus mutans* interaction with animal tissue (also human)
- R01DE-05729-01 Etiological mechanisms in periodontal disease
- R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens

IMMUNOLOGY, ANTIGENS BACTERIAL

SEE ALSO POLYSACCHARIDES, BACTERIAL (GENERAL)

- ** P50DE-02623-14 0014 Center for oral health research - Surface receptors on plaque forming organisms
- ** R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)
- R01DE-03180-11 Microbiologic studies of the human oral streptococci
- R01DE-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)
- R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)
- R01DE-04174-07 Variations in the surface structures of oral bacteria
- R01DE-04175-07 Variations in the surface structures of oral bacteria
- R01DE-04217-07 Effective immunity to dental caries--Cellular basis
- R01DE-04296-07 Lysozyme--Cell surface interactions and oral defense
- R01DE-04645-04 A genetic-biochemical analysis of spirochete motility
- P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
- P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05696-01 *Streptococcus mutans* interaction with animal tissue (also human)
- ** R01DE-05747-01 Monoclonal antibody analysis of *S. mutans* antigens
- R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens
- ** R01DE-72408-06 Cross-reacting antigens/oral flora acidogenic bacteria

IMMUNOLOGY, ANTIGENS BACTERIAL, BACTERIAL TOXINS (GENERAL)

SEE ALSO IMMUNOLOGY, ANTIGENS BACTERIAL, ENDOTOXINS
SEE ALSO IMMUNOLOGY, ANTIGENS BACTERIAL, EXOTOXINS
R01DE-04808-02 Virulence factors of gram negative corroding bacteria

IMMUNOLOGY, ANTIGENS BACTERIAL, ENDOTOXINS

- P50DE-02670-15 0018 Institute of Dental Research - Structure of human secretory immunoglobulin A
- R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)
- R01DE-05512-02 Role of macrophages in periodontal disease
- R01DE-05817-01 Gingival collagenase--Quantitation and localization (rabbits, mice, human)

IMMUNOLOGY, ANTIGENS BACTERIAL, EXOTOXINS

P50DE-02731-15 0019 Development support for dental research institute - Structure and maintenance of extrachromosomal DNA in streptococci

IMMUNOLOGY, ANTIGENS MICROBIAL

SEE ALSO IMMUNOLOGY, ANTIGENS BACTERIAL
SEE ALSO IMMUNOLOGY, ANTIGENS VIRAL
SEE ALSO MICROBIAL IDENTIFICATION AND CLASSIFICATION, SEROTYPING

- SEE ALSO POLYSACCHARIDES, BACTERIAL (GENERAL)
- P50DE-02623-14 0005 Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
- R01DE-05732-02 Specificity of cell mediated immune response in periodontal disease

IMMUNOLOGY, ANTIGENS MICROBIAL, ZYMOSAN

- R01DE-05626-01 Role of complement in periodontal disease

IMMUNOLOGY, ANTIGENS VIRAL

- P50DE-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus
- P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction
- R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)
- R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)

IMMUNOLOGY, COMPLEMENT

- SEE ALSO BACTERIOLYSIS
- R01DE-03301-11 Connective tissue of the periodontium--Collagen maturation
- R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)
- R01DE-04296-07 Lysozyme--Cell surface interactions and oral defense
- P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- ** P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)
- P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
- ** R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
- R01DE-05413-02 Bone resorption in periodontal disease
- R01DE-05414-02 The local immune response in periodontal disease (human)
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05512-02 Role of macrophages in periodontal disease
- ** R01DE-05626-01 Role of complement in periodontal disease

IMMUNOLOGY, COMPLEMENT, CHEMOTACTIC FACTORS

- P50DE-02600-15 0030 Support for oral biology research center - Leukocyte function--Its role in periodontal disease (human)
- R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)
- R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)
- ** P50DE-05139-04 0003 Clinical research center for periodontal disease

IMMUNOLOGY, COMPLEMENT RECEPTORS

- R01DE-05414-02 The local immune response in periodontal disease (human)

IMMUNOLOGY, HAPTENS

- P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction

IMMUNOLOGY, MICROBIAL

SEE ALSO IMMUNITY, BACTERIAL DEFENSES (GENERAL)
SEE ALSO IMMUNOLOGY, ANTIGENS MICROBIAL
R01DE-01554-20 Host factors in caries resistance (human, rats)

- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
- P50DE-02600-15 0035 Support for oral biology research center - Serotyping of microbes for diagnosis of periodontitis (rabbits)
- P50DE-02600-15 0037 Support for oral biology research center - Periodontal microflora (human)
- P50DE-02623-14 0005 Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- P50DE-02623-14 0032 Center for oral health research - Interactions of salivary agglutinins and oral bacteria
- P50DE-02670-15 0033 Institute of Dental Research - Genetic and biochemical basis for *S. mutans* virulence (rats)
- ** P50DE-02670-15 0037 Institute of Dental Research -
- ** R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)
- ** P50DE-04881-05 0003 Center for clinical research in periodontal diseases - Host immunologic response to oral microorganisms

- ** P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)
- R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
- ** P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations
- R01DE-05156-03 Immunoidentification of periodontal plaque bacteria
- ** R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)
- ** R01DE-05352-03 Immunochemical studies in periodontal disease
- R01DE-05359-01 Regulation of secretory immunity to *S. mutans* (mice)
- ** R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05512-02 Role of macrophages in periodontal disease
- ** R01DE-05531-03 Salivary immune factors (human, bacteria)
- ** R01DE-05626-01 Role of complement in periodontal disease
- R01DE-05706-01 Role of microbial collagenases in periodontal disease
- R01DE-05723-01 Spirochete influence on immunity in oral disease
- ** R01DE-05732-02 Specificity of cell mediated immune response in periodontal disease
- R13DE-05753-01 Symposium on host-bacteria in periodontal diseases
- R23DE-05942-01 Airway factors in cleft palate dentofacial deformity
- R23DE-05951-01 Selective microbial ecology of periodontitis siblings
- R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens

IMMUNOLOGY, SECRETORY (ANTIBODY) (FACTOR) SYSTEM

- ** P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction
- P50DE-02623-14 0026 Center for oral health research - Collagen biosynthesis in the periodontium
- P50DE-02623-14 0027 Center for oral health research - Collagenase in the periodontium
- P50DE-02670-15 0018 Institute of Dental Research - Structure of human secretory immunoglobulin A
- P50DE-02670-15 0037 Institute of Dental Research -
- ** R01DE-03420-09 Immune phenomena in experimental periodontal disease (rats)
- ** R01DE-04217-07 Effective immunity to dental caries--Cellular basis
- R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)
- ** R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)
- R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)
- ** R01DE-05359-01 Regulation of secretory immunity to *S. mutans* (mice)
- R01DE-05531-03 Salivary immune factors (human, bacteria)
- R01DE-05652-01 Biological role of lysozyme in human saliva

IMMUNOLOGY, SEROLOGY*

SEE ALSO BLOOD AND RE SYSTEM, BLOOD, SERUM
SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, AGGLUTINATION REACTION (AGGLUTININ)*
SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, HEMAGGLUTINATION*
SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNODIFFUSION TESTS*
SEE ALSO MICROBIAL IDENTIFICATION AND CLASSIFICATION, SEROTYPING

- P50DE-02623-14 0014 Center for oral health research - Surface receptors on plaque forming organisms

IMMUNOLOGY, TOXIC REACTIONS AND MECHANISMS IN IMMUNOLOGY

- ** R01DE-05696-01 *Streptococcus mutans* interaction with animal tissue (also human)

IMMUNOPATHOLOGY (GENERAL)

SEE ALSO HYPERSENSITIVITY (GENERAL)
SEE ALSO NEOPLASMS IMMUNOLOGY
SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT, GRAFT VERSUS HOST REACTIONS

- ** P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- R01DE-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)
- R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

IMMUNOPATHOLOGY, IMMUNOLOGIC DEFICIENCY DISORDERS

SEE ALSO IMMUNITY, IMMUNOLOGICAL UNRESPONSIVENESS
SEE ALSO METABOLIC DISORDERS INBORN, CHEDIAK-HIGASHI SYNDROME
R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

IMMUNOREGULATION

SEE IMMUNITY, IMMUNOREGULATION

IMMUNOSUPPRESSION

SEE IMMUNITY, IMMUNOSUPPRESSION

IMMUNOSUPPRESSION (IS) GENES

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

IMMUNOSUPPRESSIVE AGENTS

SEE IMMUNITY, IMMUNOSUPPRESSIVE AGENTS

IMMUNOTHERAPY

SEE IMMUNITY, IMMUNIZATION (IMMUNOTHERAPY)

IMP:L-ASPARTATE LIGASE (GDP)

SEE CARBON-NITROGEN LIGASES, IMP:L-ASPARTATE LIGASE (GDP)

IMPLANT COMPATIBILITY

SEE TISSUE COMPATIBILITY-TRANSPLANT, IMPLANT COMPATIBILITY

IMPLANTS

SEE TISSUE COMPATIBILITY-TRANSPLANT, IMPLANT

IMPRESSION MATERIALS

SEE DENTAL MATERIALS, IMPRESSION MATERIALS

IN

SEE METALS, HEAVY METALS, INDIUM (COMPOUNDS)

INACTIVATION POTENTIAL

SEE ELECTROPOTENTIALS

INBORN ERRORS OF METABOLISM

SEE METABOLIC DISORDERS INBORN

INBREEDING

SEE GENETICS, POPULATION GENETICS, INBREEDING

INDERAL

SEE NAPHTHYLAMINES, PROPRANOLOL

INDIUM (COMPOUNDS)

SEE METALS, HEAVY METALS, INDIUM (COMPOUNDS)

INDIVIDUALITY

SEE PSYCHOLOGY, PERSONALITY

INDOCIN

SEE BENZOPYRROLE CARBOXYLIC ACIDS, INDOMETHACIN

INDOMETHACIN

SEE BENZOPYRROLE CARBOXYLIC ACIDS, INDOMETHACIN

INDUSTRIAL HAZARD

SEE OCCUPATIONAL HEALTH, OCCUPATIONAL HAZARDS

INFANT ANIMALS

SEE AGE (ANIMAL), INFANTS

INFANT DIABETES

SEE CARBOHYDRATES METABOLISM DISORDERS, DIABETES, INSULIN-DEPENDENT DIABETES

INFANT FOODS

SEE FOOD, INFANT FOODS

INFANT HUMAN

SEE CHILDREN, INFANT (BIRTH TO 1 YR)

INFANT MENTAL DEVELOPMENT

SEE CHILD MENTAL DEVELOPMENT

INFANT NEWBORN

SEE CHILDREN, INFANT NEWBORN (BIRTH TO 4-6 WKS)

INFANT NEWBORN (ANIMAL)

SEE AGE (ANIMAL), INFANTS NEWBORN

INFANTS OF HIGHER VERTEBRATES

SEE AGE (ANIMAL), INFANTS

INFECTION MECHANISM

SEE VIRUS DISEASE CHARACTERISTICS, INFECTION MECHANISMS (GENERAL)

INFECTIOUS DISEASES CONTROL

SEE COMMUNICABLE DISEASE CONTROL

INFLAMMATION

SEE DISEASES, PATHOLOGIC PROCESSES, INFLAMMATION

INFORMATION AND COMMUNICATION, AUDIOTAPESSEE ALSO INFORMATION DISSEMINATION, VIDEOTAPES (GENERAL)
R23DE-05799-01 Behavioral methods for pedodontic management (human)**INFORMATION AND COMMUNICATION, LANGUAGES, FOREIGN**

** R01DE-05904-01 Revision of the F.D.I dental lexicon

INFORMATION AND COMMUNICATION, VOICESEE ALSO INFORMATION-COMMUNICATION BEHAVIOR, SPEECH
R01DE-03631-08 Physiological study of speech adaptation (human)**INFORMATION BANKS**

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

INFORMATION CENTERS

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

INFORMATION-COMMUNICATION BEHAVIORSEE ALSO COMMUNICATIVE SCIENCES STUDY SECTION
R01DE-04494-05 Control of stress during dental procedures (human)**INFORMATION-COMMUNICATION BEHAVIOR, FACIAL EXPRESSION**

R01DE-04990-03 Normal and abnormal faces (human)

INFORMATION-COMMUNICATION BEHAVIOR, LANGUAGE DEVELOPMENT

P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

INFORMATION-COMMUNICATION BEHAVIOR, SPEECH

SEE ALSO INFORMATION AND COMMUNICATION, VOICE

** P50DE-02668-15 0214 Regional dental research center -

Motor control during speech

P01DE-02872-12 0038 Craniofacial dysmorphology -

Evaluation of craniofacial surgery

** R01DE-03631-08 Physiological study of speech adaptation (human)

** R01DE-05203-03 Speech adaptations to orthognathic surgery (human)

INFORMATION-COMMUNICATION BEHAVIOR, VERBAL BEHAVIOR

** R01DE-03631-08 Physiological study of speech adaptation (human)

INFORMATION-COMMUNICATION DISORDERS, SPEECH DISORDERS

SEE ALSO CONGENITAL ABNORMALITIES, EAR-HEARING, DEAFNESS

P01DE-01697-19 0036 A research program in craniofacial problems - Evaluation of velopharyngeal sphincteric function (human)

** P01DE-01697-19 0037 A research program in craniofacial problems - Effects of oronasal fistulae on speech (human)

** P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate

** P01DE-05837-01 0001 Growth, surgical, and speech aspects of cleft palate - Speech pathology (human)

** P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)

R23DE-05942-01 Airway factors in cleft palate dentofacial deformity

INFORMATION-COMMUNICATION DISORDERS, SPEECH DISORDERS DIAGNOSIS

P50DE-02668-15 0214 Regional dental research center -

** P01DE-02872-12 0057 Craniofacial dysmorphology - Speech and hearing testing (human)

R01DE-05203-03 Speech adaptations to orthognathic surgery (human)

** P01DE-05837-01 0001 Growth, surgical, and speech aspects of cleft palate - Speech pathology (human)

P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)

INFORMATION-COMMUNICATION DISORDERS, SPEECH THERAPY

** R01DE-05203-03 Speech adaptations to orthognathic surgery (human)

P01DE-05837-01 0001 Growth, surgical, and speech aspects of cleft palate - Speech pathology (human)

INFORMATION DISSEMINATIONSEE ALSO INFORMATION AND COMMUNICATION, AUDIOTAPES
SEE ALSO INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

SEE ALSO PUBLICATIONS

R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)

INFORMATION DISSEMINATION, MEETINGS CONFERENCES SYMPOSIA

** R13DE-04860-01 Conference-dental implants: benefit or risk

** R01DE-05698-01 Evaluation of orthognathic surgery patients

** R13DE-05753-01 Symposium on host-bacteria in periodontal diseases

INFORMATION DISSEMINATION, MEETINGS CONFERENCES SYMPOSIA, INTERNATIONAL

** R13DE-05752-01 Conference on biology of mineralized connective tissues

** R13DE-05897-01 Oral immunogenetics and tissue transplantation (symposium)

** R13DE-05898-01 13th Annual International Biomaterials Symposium - 1981

** R13DE-05982-01 Third World Congress on Pain (Scotland)

INFORMATION DISSEMINATION, MEETINGS CONFERENCES SYMPOSIA, WORKSHOP

SEE ALSO EDUCATION, TRAINING

** R13DE-05468-01 Symposium on orthodontics and bioengineering (Connecticut)

INFORMATION DISSEMINATION, VIDEOTAPES (GENERAL)

R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)

R23DE-05799-01 Behavioral methods for pedodontic management (human)

N01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)

INFORMATION EXCHANGE

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

INFORMATION GATHERING (DATA COLLECTION)

SEE ALSO POPULATION SURVEYS

R01DE-02320-16 Clinical behavior of dental restorative materials

P01DE-02872-12 0058 Craniofacial dysmorphology - Ophthalmology (human, rabbits)

INFORMATION GATHERING (DATA COLLECTION), QUESTIONNAIRES

R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)

INFORMATION GATHERING METHODS EVALUATION-STANDARDS

** R01DE-04068-07 Statistical methods in dental research

R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)

INFORMATION PROCESSING AND CONTROL (BIOLOGICAL), HOMEOSTASIS

SEE ALSO BODY FLUID BALANCE, ACID-BASE

SEE ALSO CELL GROWTH REGULATION

SEE ALSO TEMPERATURE (BODY) REGULATION

P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)

P50DE-02668-15 0088 Regional dental research center - Hypervitaminosis D in lactation

P50DE-02668-15 0196 Regional dental research center - Cytochemical demonstration of macromolecules of craniofacial tissue

R23DE-05393-03 Factors association with hyperplasia of oral mucosa

R01DE-05395-02 Stem cells in oral mucosa

R01DE-05413-02 Bone resorption in periodontal disease

R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

R01DE-06065-01 The role of lymphoid cells in alveolar bone resorption

INFORMATION PROCESSING AND CONTROL (NEURAL)

SEE ALSO EYE, VISUAL FEEDBACK

SEE ALSO NEUROPHYSIOLOGY (GENERAL)

SEE ALSO PSYCHOBIOLOGY, PSYCHOPHYSIOLOGY

SEE ALSO SENSORY FEEDBACK

** R01DE-04884-13 Neural processes in somatic movement (monkeys)

** R23DE-05142-03 Control mechanisms in salivary gland development (rats)

R01DE-05204-03 Operant neural control in trigeminal pain systems (rat)

** R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

** R23DE-05310-03 Neural control of mandibular movement

R01DE-05558-01 Sensory alterations of craniofacial form (Rhesus monkeys)

INFORMATION RETRIEVAL

SEE INFORMATION SYSTEMS, INFORMATION RETRIEVAL

INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

SEE ALSO BIOMEDICAL SYSTEMS AUTOMATED, HEALTH CARE FACILITIES (SYSTEMS) INFORMATION SYSTEMS

SEE ALSO TISSUE (CELL) CULTURE, CELL CULTURE COLLECTIONS BANKS AND REGISTRIES

** P01DE-02872-12 0018 Craniofacial dysmorphology - Date bank-Computerization of clinical data

** P01DE-02872-12 0056 Craniofacial dysmorphology - Center for craniofacial anomalies

R01DE-05582-01 Computer graphic analysis of cranio-facial morphology

INFORMATION SYSTEMS, INFORMATION RETRIEVAL

P01DE-02872-12 0018 Craniofacial dysmorphology - Date bank-Computerization of clinical data

** P01DE-02872-12 0056 Craniofacial dysmorphology - Center for craniofacial anomalies

R01DE-05511-02 Evanston-Oak park fluoridation study after 25 years (human)

M P01DE-05837-01 Growth, surgical, and speech aspects of cleft palate

P01DE-05837-01 0001 Growth, surgical, and speech aspects of cleft palate - Speech pathology (human)

INHALATION

SEE SENSORY DEPRESSION, ANESTHESIA (GENERAL), INHALATION

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

INHALATION ANESTHESIA

SEE SENSORY DEPRESSION, ANESTHESIA (GENERAL),
INHALATION

INHALATION-EXHALATION

SEE RESPIRATORY FUNCTION, RESPIRATION

INHIBITORS

SEE CALCIFICATION INHIBITORS (CALCIUM NEGATIVE BALANCE
DRUGS)

SEE DENTAL CARIES INHIBITORS

SEE ENZYME INHIBITORS

SEE GROWTH INHIBITORS

SEE NUCLEIC ACIDS INHIBITORS

INJURIES, FRACTURES

R01DE-04327-06 Mechanical and electrical effects on
osteogenesis (chick embryo)

R01DE-04629-05 Dental disease and osteoclastic bone
resorption (chick embryo, quail)

INJURIES, FRACTURES, JAW

** R01DE-02212-13 Circulation in teeth and supporting
structures (dogs, monkeys)

R01DE-04610-03 Physiological studies on mastication
(human)

INJURIES, SCARS

SEE ALSO SKIN DISORDERS, KELOID

R01DE-05459-02 Phenytoin-Pathogenesis of gingival
overgrowth (cats)

P01DE-05837-01 0002 Growth, surgical, and speech aspects
of cleft palate - Maxillofacial growth (dogs, tamarins)

INJURIES, SURGICAL WOUNDS

P01DE-05837-01 0002 Growth, surgical, and speech aspects
of cleft palate - Maxillofacial growth (dogs, tamarins)

INJURIES, TRAUMA

P50DE-02731-15 0001 Development support for dental
research institute - Functional disturbances of the masticatory
system (human)

P50DE-02731-15 0033 Development support for dental
research institute - Clinical trials of periodontal therapy

R01DE-05636-01 Cellular mediators in tooth maintenance and
repair (rats)

INJURIES, WOUND HEALING

SEE ALSO GROWTH AND DEVELOPMENT, REGENERATION

R01DE-02212-13 Circulation in teeth and supporting
structures (dogs, monkeys)

P50DE-02731-15 0033 Development support for dental
research institute - Clinical trials of periodontal therapy

** R01DE-03794-09 Surgical-orthodontics and bone healing
(monkeys)

R01DE-04338-06 Characterization of oral mucosa and skin
basal lamina (human, animals)

R01DE-04629-05 Dental disease and osteoclastic bone
resorption (chick embryo, quail)

R01DE-05109-02 Composite bone grafts in dentistry and
medicine

** P01DE-05837-01 0002 Growth, surgical, and speech aspects
of cleft palate - Maxillofacial growth (dogs, tamarins)

INJURY (HAZARDS) PREVENTION AND**CONTROL, BIOHAZARDS (CONTROL)**

R23DE-05507-02 Psychomotor impairment related to N2O
exposure (human)

INJURY (HAZARDS) PREVENTION AND**CONTROL, SAFETY EQUIPMENT-****ENGINEERING**

R01DE-04783-04 The development of a dental x-ray aiming
device

INNERVATION (GENERAL)

SEE NERVOUS SYSTEM, NERVES, INNERVATION (GENERAL)

INOTROPIC AGENTS POSITIVE

SEE MUSCLE STIMULANTS

INSPIRATION-EXPIRATION

SEE RESPIRATORY FUNCTION, RESPIRATION

INSTRUMENTATION CLINICALLY ORIENTED

SEE BIOMEDICAL ENGINEERING, INSTRUMENTATION CLINICALLY
ORIENTED

INSTRUMENTS AND EQUIPMENT (HARDWARE)

SEE BIOMEDICAL ENGINEERING

SEE BIOMEDICAL SYSTEMS AUTOMATED

SEE DENTAL INSTRUMENTS*

SEE INJURY (HAZARDS) PREVENTION AND CONTROL, SAFETY
EQUIPMENT-ENGINEERING

INSULIN

SEE PANCREAS HORMONES, INSULIN

INSULIN-DEPENDENT DIABETES

SEE CARBOHYDRATES METABOLISM DISORDERS, DIABETES,
INSULIN-DEPENDENT DIABETES

INSURANCE

SEE HEALTH INSURANCE, DENTAL

INTEGRATIVE CONTROL (NEURAL)

SEE INFORMATION PROCESSING AND CONTROL (NEURAL)

INTELLIGENCE, ARTIFICIAL

SEE COMPUTER, ARTIFICIAL INTELLIGENCE, PATTERN
RECOGNITION AND CONTROL SYSTEMS

INTERACTIONS

SEE DRUGS AND PHYSICAL AND/OR CHEMICAL AGENTS

INTERACTION

SEE DRUGS INTERACTION

SEE NUTRIENTS AND PHYSICAL AND/OR CHEMICAL AGENTS

INTERACTION

SEE PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION

(BIOLOGICAL AND ECOLOGICAL)

INTERCELLULAR BRIDGES, CONNECTIONS

SEE CELL-CELL INTERACTION, INTERCELLULAR CONNECTIONS-
JUNCTIONS

INTERCELLULAR JUNCTIONS

SEE CELL-CELL INTERACTION, INTERCELLULAR CONNECTIONS-
JUNCTIONS

INTERCELLULAR SPACE

SEE BODY FLUIDS, EXTRACELLULAR SPACE (COMPARTMENT)

INTERFACIAL PHENOMENA WITH**BIOMATERIALS**

SEE BIOMATERIALS, INTERFACIAL PHENOMENA

INTERNAL CONTROL (AUTOGENIC**CONDITIONING)**

SEE PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL
CONTROL

INTERNAL RESPIRATION

SEE RESPIRATION INTERNAL

INTERNATIONAL MEETINGS

SEE INFORMATION DISSEMINATION, MEETINGS CONFERENCES
SYMPOSIA, INTERNATIONAL

INTERNEURONS

SEE NERVOUS SYSTEM, NEURONS, INTERNEURONS

INTERPERSONAL BEHAVIOR, RELATIONS

SEE PSYCHOLOGY SOCIAL, INTERPERSONAL RELATIONS

INTERVAL OF STIMULUS

SEE STIMULUS INTERVAL

INTESTINES

SEE GASTROINTESTINAL SYSTEM, INTESTINES

INTRINSIC SURFACE ACTIVITY OF MEMBRANES

SEE MEMBRANE SURFACE (BIOLOGICAL) ACTIVITY (GENERAL)

INVERTASE

SEE CARBOHYDRASES, BETA-FRUCTOFURANOSIDASE

INVERTIN

SEE CARBOHYDRASES, BETA-FRUCTOFURANOSIDASE

INVESTMENT, INVESTMENT MATERIALS,**DENTAL**

SEE DENTAL MATERIALS, INVESTMENT

IODIDES

SEE HALOGENS, IODINE (COMPOUNDS) SEE ALSO SPECIFICS

IODINE (COMPOUNDS)

SEE HALOGENS, IODINE (COMPOUNDS) SEE ALSO SPECIFICS

ION CARRIERS

SEE BIOLOGICAL TRANSPORT, ION EXCHANGE AND TRANSPORT,
ION CARRIERS (IONOPHORES)

ION EXCHANGE AND TRANSPORT

SEE BIOLOGICAL TRANSPORT, ION EXCHANGE AND TRANSPORT

ION PUMPS

SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS

ION PUMP INHIBITORS

SEE BIOLOGICAL TRANSPORT, TRANSPORT EFFECTORS

IONIC BONDS

SEE CHEMICAL BONDS, IONIC

IONIC CONDUCTANCE CHANNELS

SEE BIOLOGICAL TRANSPORT, MEMBRANE PERMEABILITY AND
TRANSPORT

IONIZING RADIATION

SEE RADIATION, IONIZING RADIATION

IONOPHORES

SEE BIOLOGICAL TRANSPORT, ION EXCHANGE AND TRANSPORT,
ION CARRIERS (IONOPHORES)

IONS

R01DE-01374-21 Matrix component interactions in calcified
tissues (cattle, rats, chickens, h

R01DE-01830-19 Quantitation of enamel demineralization
mechanisms

R01DE-04835-03 Anti-carries mechanism of fluoride complexes
in vitro (human)

IONS, ANION

R01DE-04385-06 Mechanism of dental caries (human)

IONS, CATION

R01DE-04008-07 Cellular and developmental control of
calcification (tissue culture)

R01DE-04385-06 Mechanism of dental caries (human)

R01DE-04486-04 Kinetics and mechanisms of action of
fluorides

R01DE-04903-03 Trace metal uptake in cariogenic
streptococcus mutans

R01DE-05390-03 Opiate action on CNS terminals of tooth pulp
fibers (animals)

R01DE-05652-01 Biological role of lysozyme in human saliva

** R23DE-05777-01 Cationic protein in submandibular saliva
(goats, rabbits, human)

IONS, ELECTROLYTES

R01DE-02110-17 Salivary gland structure and function (rats)

P50DE-02600-15 0034 Support for oral biology research
center - Salivary and oral mucosal changes after cancer
chemotherapy

R01DE-03601-09 Localized corrosion of dental amalgam

R01DE-04897-02 Functional development of salivary glands
(rats)

R01DE-05483-02 Characterization of predentinal extracellular
fluid (rats)

IONS, POLYIONS, POLYANIONS

R01DE-05251-02 Salivary gland secretory mechanisms (rats)

IRON

SEE ALSO ALBUMINS, CONALBUMIN

SEE ALSO METALLOPROTEINS, LACTOFERRIN

SEE ALSO METALLOPROTEINS, TRANSFERRIN

SEE ALSO NUTRITION, DIETARY CONSTITUENTS, DIETARY IRON

R01DE-04252-07 Semi and nonprecious metal-porcelain
systems

R23DE-05628-02 Influence of trace metals on dental health
(rat)

IRON, DIETARY

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY IRON

IRON-BINDING BETA1-GLOBULIN (SERUM)

SEE METALLOPROTEINS, TRANSFERRIN

IRON METABOLISM

SEE ALSO NUTRITION, DIETARY CONSTITUENTS, DIETARY IRON

** P01DE-01850-18 0072 Nutritional sources and metabolic
roles of fluoride - Effect of fluoride on iron transport (mice)

P50DE-02670-15 0035 Institute of Dental Research -
Granulocyte growth and division

R01DE-05722-02 Bactericidal activity of lactoferrin on oral
flora

IRRIGATION (BODY)

SEE THERAPY, LAVAGE

IS GENES

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

ISOALLOANTIGENS

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS
(HISTOCOMPATIBILITY ANTIGENS)

ISOALLOIMMUNITY

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOIMMUNITY

ISOANTIGENS

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS
(HISTOCOMPATIBILITY ANTIGENS)

ISOENZYMES

SEE ENZYMES, ISOENZYMES

ISOIMMUNITY

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOIMMUNITY

ISOPROTERENOL

SEE PHENYLALKYLAMINES, CATECHOLAMINES, ISOPROTERENOL

ISUPREL

SEE PHENYLALKYLAMINES, CATECHOLAMINES, ISOPROTERENOL

IZ-1 GENES

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

IZ-2 GENES

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

J CHAIN LOCUS

SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND
CONTROL

JACKBEAN AGGLUTININ (LECTIN)

SEE PLANTS PROTEINS, LECTINS, CONCAVALIN A

JAW

SEE ORAL-PHARYNGEAL, JAW

JAW FRACTURES

SEE INJURIES, FRACTURES, JAW

JAW MOVEMENT

SEE ORAL-PHARYNGEAL, JAW MOVEMENT

JOB PERFORMANCE

SEE OCCUPATIONS, JOB PERFORMANCE

JOINT DISORDERS

SEE SKELETAL DISORDERS, JOINT DISORDERS

JOINT STRESS

SEE SKELETAL STRESS

JUVENILE (HUMAN)

SEE CHILDREN, ADOLESCENCE (12 TO 21 YRS)

JUVENILE DIABETES

SEE CARBOHYDRATES METABOLISM DISORDERS, DIABETES,
INSULIN-DEPENDENT DIABETES

(contd.)

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JUVENILE RHEUMATOID ARTHRITIS
SEE SKELETAL DISORDERS, ARTHRITIS, RHEUMATOID

K
SEE POTASSIUM

K-CELLS
SEE BLOOD CELLS, LYMPHOCYTES, KILLER CELLS

KALLIDIN-9
SEE PEPTIDES, VASOACTIVE PEPTIDES, KALLIDIN-9

KANAMYCIN
SEE ANTIBIOTICS, AMINOGLYCOSIDE ANTIBIOTICS, KANAMYCIN

KAPPA CHAIN (LIGHT CHAIN)
SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL

KELOID
SEE SKIN DISORDERS, KELOID

KERATIN
SEE ALBUMINOIDS, KERATIN

KERATINIZATION (GENERAL)
SEE GROWTH AND DEVELOPMENT, KERATINIZATION

KERATINIZATION ABNORMAL
SEE GROWTH ABNORMAL, KERATINIZATION ABNORMAL

KERATOHYALIN
SEE ALBUMINOIDS, KERATOHYALIN

KERATOSIS, SKIN
SEE SKIN DISORDERS, SKIN KERATOSIS

KERN GENES
SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL

KETOACIDS
SEE CARBOXYLIC ACIDS, KETO ACIDS

KETOSIS-PRONE DIABETES
SEE CARBOHYDRATES METABOLISM DISORDERS, DIABETES, INSULIN-DEPENDENT DIABETES

KIDNEY
** R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

KIDNEY, GLOMERULUS
R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

KIDNEY DISORDERS, RENAL RICKETS
SEE ALSO METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN
R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

KIDNEY DISORDERS, UREMIA
R01DE-05413-02 Bone resorption in periodontal disease

KIDNEY FUNCTION, RENAL TUBULAR TRANSPORT
R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

KILLER CELLS
SEE BLOOD CELLS, LYMPHOCYTES, KILLER CELLS

KINESTHESIS
SEE SENSORY-PERCEPTUAL PROCESSES, PROPRIOCEPTION

KINETICS (CHEMISTRY)
SEE CHEMICAL REACTIONS (DYNAMICS)

KORNBERG'S DARK REPAIR ENZYME
SEE NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)

KREBS CYCLE
SEE TRICARBOXYLIC ACIDS, KREBS CYCLE

L-CHAIN GENETICS
SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL

LABORATORY (BIOMEDICAL) DATA COMPUTER PROCESSING
SEE BIOMEDICAL SYSTEMS AUTOMATED, COMPUTER PROCESSING OF LABORATORY DATA (GENERAL)

LABORATORY FACILITIES
SEE BIOMEDICAL FACILITIES

LACTATE DEHYDROGENASE
SEE OXIDOREDUCTASES, LACTATE DEHYDROGENASE

LACTATES
SEE FATTY ACIDS, LACTATES

LACTATION
SEE REPRODUCTIVE SYSTEM FEMALE, MAMMARY GLANDS, LACTATION

LACTOBACILLUS
SEE BACTERIA, LACTOBACILLACEAE, LACTOBACILLUS*

LACTOFERRIN
SEE METALLOPROTEINS, LACTOFERRIN

LACTOPEROXIDASE
SEE PEROXIDASES, LACTOPEROXIDASE

LACTOSE
SEE DISACCHARIDES, LACTOSE

LAD GENE
SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

LAMBDA CHAIN (LIGHT CHAIN)
SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL

LANGUAGE DEVELOPMENT
SEE INFORMATION-COMMUNICATION BEHAVIOR, LANGUAGE DEVELOPMENT

LANGUAGES, FOREIGN
SEE INFORMATION AND COMMUNICATION, LANGUAGES, FOREIGN

LARGE LYMPHOCYTE DEPENDENT IMMUNE SYSTEM
SEE IMMUNITY, HUMORAL IMMUNITY

LARYNGEAL NERVES
SEE NERVOUS SYSTEM, CRANIAL NERVES, LARYNGEAL NERVES

LARYNX
SEE RESPIRATORY SYSTEM, LARYNX

LATENT VIRUS DISEASES
SEE VIRUS DISEASE CHARACTERISTICS, LATENT DORMANT OR SLOW

LAVAGE
SEE THERAPY, LAVAGE

LEAD POISONING
SEE METALS POISONING, LEAD POISONING

LECITHINASE A
SEE PHOSPHOLIPASE, LECITHINASE A

LECTINS
SEE PLANTS PROTEINS, LECTINS

LEPTOSPIRA
SEE BACTERIA, SPIROCHETES, LEPTOSPIRA*

LEPTOTRICHIA
SEE BACTERIA, ACTINOMYCETALES, LEPTOTRICHIA*

LETS PROTEIN
SEE GLYCOPROTEINS, FIBRONECTIN

LEUKEMIA
SEE NEOPLASMS OF BLOOD AND RE SYSTEM, LEUKEMIA

LEUKOCYTES
SEE BLOOD CELLS, LEUKOCYTES

LEUKOPENIA
SEE BLOOD AND RE DISORDERS, LEUKOCYTE DISORDERS, LEUKOPENIA

LEUKOPLAKIA ORAL
SEE ORAL-PHARYNGEAL HYPERPLASIA, LEUKOPLAKIA ORAL

LEUKOSIS (LYMPHOMATOSIS) VIRUSES AVIAN
SEE VIRUSES, RETROVIRIDAE, LEUKOSIS-SARCOMA AVIAN, LEUKOSIS VIRUSES AVIAN

LEUKOTAXIC FACTOR
SEE HYPERSENSITIVITY, LYMPHOKINES, LEUKOTAXIC FACTOR

LEUKOVIRUSES
SEE VIRUSES, RETROVIRIDAE

LEVANS
SEE HEXOSANS, LEVANS

LEVARTERENOL
SEE PHENYLALKYLAMINES, CATECHOLAMINES, NOREPINEPHRINE

LEVULOSE
SEE HEXOSES, FRUCTOSE

LI
SEE METALS, ALKALI METALS, LITHIUM

LIBRARY (BIOMEDICAL) REVIEW COMMITTEE
** R01DE-05904-01 Revision of the F.D.I dental lexicon

LIGAMENTS
SEE SKELETAL SYSTEM, LIGAMENT

LIGANDS
SEE METAL COMPLEXES, LIGANDS

LIGHT
SEE PHOTOCHEMISTRY

LIGHT POLARIZATION
SEE OPTICAL POLARIZATION*

LIGHT SCATTERING
SEE OPTICS, LIGHT SCATTERING*

LIMBS ARTIFICIAL
SEE SKELETAL DISORDERS, ORTHOPEDICS, LIMBS ARTIFICIAL

LINKAGE
SEE GENETIC MAPPING, LINKAGE

LIP
SEE ORAL-PHARYNGEAL, LIPS

LIP, CLEFT
SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CLEFT LIP

LIP NEOPLASMS
SEE NEOPLASMS OF ORAL-PHARYNGEAL STRUCTURES, LIP NEOPLASMS

LIPID METABOLISM
SEE LIPIDS METABOLISM

LIPIDS
SEE ALSO ENDOCRINOLOGY, HORMONES, STEROID HORMONES
SEE ALSO GLYCOLIPIDS
SEE ALSO LIPOPROTEINS
SEE ALSO NUTRITION, DIETARY CONSTITUENTS, DIETARY LIPIDS
SEE ALSO PHOSPHOLIPIDS
SEE ALSO POLYSACCHARIDES, LIPOPOLYSACCHARIDES
SEE ALSO PROTEOLIPIDS
SEE ALSO STEROIDS
SEE ALSO TRIOSE ALCOHOLS, GLYCERIN
P50DE-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins
R01DE-04844-04 Stress-related bone resorption--Mechanisms of action (rats)
R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)
** R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)

LIPIDS, DIETARY
SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY LIPIDS

LIPIDS, GLYCERIDES, DIGLYCERIDES
R01DE-05592-02 Biochemistry of salivary lipids (monkeys, rats, human)

LIPIDS, GLYCERIDES, TRIGLYCERIDES
R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)

LIPIDS, MEMBRANE LIPIDS
SEE ALSO PHOSPHOLIPIDS
R01DE-04175-07 Variations in the surface structures of oral bacteria
R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

LIPIDS, OILS, CROTON OIL
R23DE-05393-03 Factors association with hyperplasia of oral mucosa

LIPIDS METABOLISM
SEE ALSO STEROID METABOLISM
R01DE-04141-07 Mechanism of hard tissue mineralization (human, rats)
R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

LIPOCHONDRODYSTROPHY
SEE METABOLIC DISORDERS INBORN, MUCOPOLYSACCHARIDOSIS, LIPOCHONDRODYSTROPHY

LIPOPOLYSACCHARIDES
SEE POLYSACCHARIDES, LIPOPOLYSACCHARIDES

LIPOPROTEINS
SEE ALSO PROTEOLIPIDS
** R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues

LIPOPROTEINS TRANSPORT
SEE PROTEINS TRANSPORT

LIPOSOMES
SEE BIOLOGICAL TRANSPORT, MEMBRANE MODELS, LIPOSOMES

LIPS
SEE ORAL-PHARYNGEAL, LIPS

LIQUID FLOW
SEE PHYSICAL PROPERTIES, FLUID FLOW

LITHIUM
SEE METALS, ALKALI METALS, LITHIUM

LIVE VACCINES
SEE VACCINES, LIVE

LIVER CELLS
R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism

LIVER DISORDERS, TOXIC LIVER DISORDERS, HEPATOTOXINS
R01DE-05466-03 Biochemical studies of a sweetener, SRI Oxime V (rats, mice, dogs, monkeys)

LIVER METABOLISM
R01DE-05466-03 Biochemical studies of a sweetener, SRI Oxime V (rats, mice, dogs, monkeys)

LIVER TOXINS
SEE LIVER DISORDERS, TOXIC LIVER DISORDERS, HEPATOTOXINS

LOCAL APPLICATION
SEE DOSAGE AND ROUTE, TOPICAL APPLICATION

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LOCAL HORMONES

SEE NEUROTRANSMITTERS AND NEUROMODULATORS (GENERAL)

LOCOMOTION IN SINGLE CELL AND MULTICELLULAR MICROORGANISMS

SEE CELL COMPONENTS, CILIARY AND FLAGELLAR MOVEMENT
SEE CELL MOVEMENT

LONG CHAIN COMPOUNDS

SEE CHEMICAL STRUCTURE, CHAIN LENGTH

LONGITUDINAL STUDY

SEE POPULATION STUDIES HUMAN, LONGITUDINAL STUDY

LONGITUDINAL STUDY, ANIMAL

SEE POPULATION STUDIES ANIMAL, LONGITUDINAL STUDY

LOW BIRTH WEIGHT, HUMAN

SEE CHILDREN, INFANT PREMATURE AND LOW BIRTH WEIGHT

LTF (LYMPHOKINES)

SEE HYPERSENSITIVITY, LYMPHOKINES, LYMPHOCYTE TRANSFORMING FACTORS

LUMINESCENCE

SEE OPTICS, LIGHT EMISSION, LUMINESCENCE*

LUNG ALVEOLUS

SEE RESPIRATORY SYSTEM, LUNG ALVEOLUS

LUPUS ERYTHEMATOSUS SYSTEMIC

SEE CONNECTIVE TISSUE DISORDERS, LUPUS ERYTHEMATOSUS SYSTEMIC

LY ANTIGEN

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

LY GENE

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

LYMPH NODES

SEE BLOOD AND RE SYSTEM, LYMPHATIC TISSUE, LYMPH NODES

LYMPHATIC TISSUE

SEE BLOOD AND RE SYSTEM, LYMPHATIC TISSUE

LYMPHOCYTE ACTIVATING FACTOR

SEE MITOGENS

LYMPHOCYTE ACTIVATION

SEE IMMUNITY, CELLULAR, LYMPHOCYTE ACTIVATION, TRANSFORMATION AND PROLIFERATION

LYMPHOCYTE PRODUCTS

SEE HYPERSENSITIVITY, LYMPHOKINES

LYMPHOCYTE PROLIFERATION

SEE IMMUNITY, CELLULAR, LYMPHOCYTE ACTIVATION, TRANSFORMATION AND PROLIFERATION

LYMPHOCYTE RECEPTORS AND RECOGNITION

SEE IMMUNITY, CELLULAR, LYMPHOCYTE ACTIVATION, TRANSFORMATION AND PROLIFERATION

LYMPHOCYTE TRANSFORMATION

SEE IMMUNITY, CELLULAR, LYMPHOCYTE ACTIVATION, TRANSFORMATION AND PROLIFERATION

LYMPHOCYTE TRANSFORMING FACTORS

SEE HYPERSENSITIVITY, LYMPHOKINES, LYMPHOCYTE TRANSFORMING FACTORS

LYMPHOCYTES

SEE BLOOD CELLS, LYMPHOCYTES

B LYMPHOCYTES

SEE BLOOD CELLS, B LYMPHOCYTES

T LYMPHOCYTES

SEE BLOOD CELLS, T LYMPHOCYTES

LYMPHOID TISSUE

SEE BLOOD AND RE SYSTEM, LYMPHATIC TISSUE

LYMPHOKINES

SEE HYPERSENSITIVITY, LYMPHOKINES

LYMPHOMA

SEE NEOPLASMS OF BLOOD AND RE SYSTEM, LYMPHOMA

LYMPHOTOXIN, LYMPHOTOXIC FACTOR

SEE HYPERSENSITIVITY, LYMPHOKINES, LYMPHOTOXIN

LYSINE

SEE DIAMINE ACIDS, LYSINE

LYSOSOMES

SEE CELL COMPONENTS, LYSOSOMES

LYSOZYME

SEE CARBOHYDRASES, LYSOZYME

MACROMOLECULES

SEE MOLECULES, MACROMOLECULES

MACROPHAGES

SEE BLOOD AND RE SYSTEM, MACROPHAGES

MAGNESIUM (COMPOUNDS)

SEE METALS, ALKALINE EARTH METALS, MAGNESIUM

MAJOR HISTOCOMPATIBILITY COMPLEX**(LOCUS)**

SEE IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)

MALE

SEE SEX, MALE

MALNUTRITION

SEE NUTRITIONAL ABNORMALITIES, MALNUTRITION (GENERAL)

MALOCCUSION

SEE DENTAL DISORDERS, MALOCCUSION

MALTOSE

SEE DISACCHARIDES, MALTOSE

MAMMALIAN GENETICS STUDY SECTION

** R01DE-03658-17 Genetic polymorphisms of saliva (human)

MAMMALS, PRIMATES*

** R01DE-04531-04 Strain in the facial bones of (primates)

MAMMALS, RODENTS, MYOMORPHA, MICE (LABORATORY)*

** P50DE-02668-15 0213 Regional dental research center - Hormone action is the salivary glands of inbred mice

MAMMALS, RODENTS, MYOMORPHA, RATS (LABORATORY)*

R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)

MANDIBLE

SEE ORAL-PHARYNGEAL, JAW, MANDIBLE

MANDIBULAR CONDYLE

SEE ORAL-PHARYNGEAL, JAW, MANDIBULAR CONDYLE

MANGANESE (COMPOUNDS)

SEE METALS, HEAVY METALS, MANGANESE (COMPOUNDS)

MAPPING

SEE GENETIC MAPPING

MARFAN SYNDROME

SEE METABOLIC DISORDERS INBORN, MARFAN SYNDROME

MARINE ORGANISMS

SEE WATER ENVIRONMENT, AQUATIC ORGANISMS, MARINE*

MARKERS

SEE GENETIC MAPPING, GENETIC MARKERS

MASTICATION

SEE DENTISTRY, MASTICATION

MATERNAL-FETAL

SEE PREGNANCY IMMUNOLOGY

MATERNAL INHERITANCE

(EXTRACHROMOSOMAL)
SEE GENETICS, EXTRACHROMOSOMAL INHERITANCE

MATERNAL NUTRITION

SEE NUTRITION, MATERNAL-FETAL NUTRITION

MATHEMATICAL MODELS

SEE MODELS, MATHEMATICAL

MATHEMATICS, STATISTICS (INCLUDING**BIOMETRY)**

SEE ALSO BODY PHYSICAL CHARACTERISTICS, CEPHALOMETRY

SEE ALSO POPULATION STUDIES HUMAN

R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)

** R01DE-04068-07 Statistical methods in dental research

** R01DE-05868-01 Multivariate analysis of craniofacial growth in clefting

MATURE ANIMAL

SEE AGE (ANIMAL), MATURE (ADULT)

MCG GENES

SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL

MEAT

SEE FOOD, MEAT

MECHANICAL PRESSURE

SEE PHYSICAL PROPERTIES, MECHANICAL PRESSURE

MECHANICAL VIBRATIONS

SEE PHYSICAL PROPERTIES, MECHANICAL VIBRATIONS

MEDICAL AUDIT

SEE HEALTH CARE QUALITY

MEDICAL EQUIPMENT SAFETY

SEE BIOMEDICAL ENGINEERING, MEDICAL EQUIPMENT SAFETY

MEDICAL RESEARCH

SEE HEALTH SCIENCES RESEARCH (GENERAL)*

MEDICINAL CHEMISTRY STUDY SECTION

** R01DE-05476-02 Novel peptide derived sweeteners

MEDICINE

SEE ANIMALS, VETERINARY MEDICINE

SEE BEHAVIORAL MEDICINE

SEE GENERAL MEDICINE STUDY SECTION

MEDROXYPROGESTERONE ACETATE

SEE PROGESTERONE ANALOGS, MEDROXYPROGESTERONE ACETATE

MEETINGS CONFERENCES SYMPOSIA

SEE INFORMATION DISSEMINATION, MEETINGS CONFERENCES SYMPOSIA

MEGACOLON CONGENITAL IDIOPATHIC

SEE CONGENITAL ABNORMALITIES, GASTROINTESTINAL, MEGACOLON CONGENITAL

MEGAKARYOCYTES

SEE BLOOD AND RE SYSTEM, MEGAKARYOCYTES

MEGAVITAMIN THERAPY

SEE NUTRITION, DIET THERAPEUTIC, VITAMIN THERAPY (ALL ROUTES OF ADMINISTRATION)

MELANOMA

SEE PIGMENT CELL NEOPLASMS, MELANOMA

MEMBRANE, BASEMENT MEMBRANE

P50DE-02670-15 0019 Institute of Dental Research - Chemistry and molecular biology of the connective tissue protein, collagen

P50DE-02731-15 0032 Development support for dental research institute - Epithelial cell basal lamina biosynthesis (rats)

** R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)

R01DE-05630-01 Matrix/cell surface in neural crest cell morphogenesis (mice, chick, quail)

R23DE-05793-01 Degradation of collagen in inflammation (human gingiva)

MEMBRANE, MEMBRANE (BIOLOGICAL) STRUCTURE

** R01DE-04174-07 Variations in the surface structures of oral bacteria

** R01DE-04175-07 Variations in the surface structures of oral bacteria

** R01DE-04296-07 Lysozyme-Cell surface interactions and oral defense

R01DE-05190-03 Factors determining variation in adult oral mucosa

R01DE-05367-02 Cranio-facial anomalies in the oel mouse

R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

MEMBRANE, MUCOUS MEMBRANE

R01DE-01554-20 Host factors in caries resistance (human, rats)

** P50DE-02600-15 0032 Support for oral biology research center - Keratohyalin in keratinization of oral mucosa and skin (human, rats)

P01DE-02847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria

** R01DE-03318-10 The molecular nature of gingival and mucosal collagen (rat)

R01DE-04039-04 Sex steroid metabolism in oral tissues

** R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)

R01DE-04660-06 Keratohyalin in keratinization--Oral mucosa and skin (human)

** R23DE-05393-03 Factors association with hyperplasia of oral mucosa

** R01DE-05395-02 Stem cells in oral mucosa

** R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)

R01DE-05531-03 Salivary immune factors (human, bacteria)

MEMBRANE (BIOLOGICAL) STRUCTURE

SEE MEMBRANE, MEMBRANE (BIOLOGICAL) STRUCTURE

MEMBRANE LIPIDS

SEE LIPIDS, MEMBRANE LIPIDS

MEMBRANE PERMEABILITY AND TRANSPORT

SEE BIOLOGICAL TRANSPORT, MEMBRANE PERMEABILITY AND TRANSPORT

MEMBRANE POTENTIALS

SEE ELECTROPOTENTIALS, MEMBRANE POTENTIALS

MEMBRANE PROTEINS

SEE PROTEINS, MEMBRANE PROTEINS

MEMBRANE SURFACE (BIOLOGICAL) ACTIVITY (GENERAL)

SEE ALSO CELL ADHESION

SEE ALSO CELL-CELL INTERACTION, CELL AGGREGATION

SEE ALSO IMMUNOLOGY, ANTIGENS, SURFACE ANTIGENS

(GENERAL)

P50DE-02623-14 0014 Center for oral health research - Surface receptors on plaque forming organisms

P50DE-02623-14 0033 Center for oral health research - Immune system in regulation of angiogenesis

P50DE-02668-15 0168 Regional dental research center - Thrombin-platelet interactions (human)

P50DE-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins

P50DE-02670-15 0025 Institute of Dental Research - Biochemical basis for the cariogenic property of Streptococcus mutans (rat)

R01DE-03180-11 Microbiologic studies of the human oral streptococci

(contd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

- R01DE-03301-11 Connective tissue of the periodontium--Collagen maturation
- ** R01DE-03654-09 Molecular basis of dental caries (human)
- ** R01DE-04174-07 Variations in the surface structures of oral bacteria
- ** R01DE-04175-07 Variations in the surface structures of oral bacteria
- R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)
- ** R01DE-04296-07 Lysozyme--Cell surface interactions and oral defense
- R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
- R01DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins
- R01DE-04614-05 Adherence of oral streptococci to hydroxyapatite
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- ** R01DE-05017-03 Characterization of surface antigens of S mutants
- R01DE-05041-03 Orofacial anomalies in phenytoin teratogenesis (mice, human)
- ** R23DE-05062-03 Tissue interactions during odontogenesis
- R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)
- R01DE-05180-03 Composition of S mutants in different growth environments
- R01DE-05190-03 Factors determining variation in adult oral mucosa
- R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)
- R01DE-05352-03 Immunochemical studies in periodontal disease
- R01DE-05354-04 Prevention of dental caries (rats, human)
- R01DE-05427-01 Adherence mechanisms of oral microbes
- R23DE-05429-03 Adherence of periodontal disease-associated bacteria
- R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence
- R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)
- R23DE-05501-02 Platelet-Streptococcal interactions in endocarditis (human, rabbits)
- R01DE-05531-03 Salivary immune factors (human, bacteria)
- ** R01DE-05586-01 Cell surface studies of the enamel organ (mice)
- R01DE-05606-02 Pili of S sanguis and their role in adhesion (human, rabbits)
- R01DE-05632-01 Development of salivary gland secretory function (rats)
- R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
- R01DE-05732-02 Specificity of cell mediated immune response in periodontal disease
- ** R01DE-05747-01 Monoclonal antibody analysis of s. mutants antigens
- R01DE-05773-01 Ligand receptor interactions of cariogenic bacteria
- R01DE-05838-02 Morphogenetic role of glycosaminoglycans (chick embryo)
- R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens

MENTAL SET

SEE PSYCHOLOGY, ATTITUDES (AND RELATED)

MERCURIALS

SEE METALS, HEAVY METALS, MERCURY (COMPOUNDS)

MERCURY (COMPOUNDS)

SEE METALS, HEAVY METALS, MERCURY (COMPOUNDS)

MESENCEPHALON

SEE BRAIN, MESENCEPHALON

MESENCHYME

SEE CONNECTIVE TISSUE, MESENCHYME

MESSANGER RIBONUCLEIC ACID

SEE NUCLEIC ACIDS, MRNA

METABOLIC BONE DISEASE

SEE SKELETAL DISORDERS, BONE METABOLISM (GENERAL)

METABOLIC DISORDERS INBORN

SEE ALSO CONGENITAL ABNORMALITIES

R13DE-05752-01 Conference on biology of mineralized connective tissues

METABOLIC DISORDERS INBORN, CHEDIAK-HIGASHI SYNDROME

R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)

METABOLIC DISORDERS INBORN, CYSTIC FIBROSIS

R01DE-01554-20 Host factors in caries resistance (human, rats)

R01DE-04971-03 Human salivary antigens--Characterization (monkeys)

R23DE-05316-03 Salivary calcium binding proteins and oral disease

R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)

R01DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)

** R23DE-05789-01 IgA receptor bearing oral cells in cystic fibrosis (human)

METABOLIC DISORDERS INBORN, EHLERS-DANLOS SYNDROME

P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)

METABOLIC DISORDERS INBORN, MARFAN SYNDROME

P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)

METABOLIC DISORDERS INBORN, MUCOPOLYSACCHARIDOSIS, LIPOCHONDRODYSOTROPHY

R01DE-05078-05 Craniofacial growth and remodeling (human)

METABOLIC DISORDERS INBORN, OSTEOGENESIS IMPERFECTA

** P01DE-01850-18 0084 Nutritional sources and metabolic roles of fluoride - Enamel, dentin and cementum in osteogenesis imperfecta (human)

P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)

METABOLIC DISORDERS INBORN, OSTEOPETROSIS

P50DE-02668-15 0176 Regional dental research center - Collagen biochemistry and the myeloblastosis associated virus infected cells

** R01DE-05351-02 Electron optical examination of mineralized tissues (animals)

R01DE-05413-02 Bone resorption in periodontal disease

METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN

** R01DE-05024-03 Craniofacial abnormalities in mice with vitamin D resistant rickets

METABOLISM, BIOTRANSFORMATION

SEE ALSO TOXICOLOGY, TOXICANT METABOLISM, DETOXICATION

N01DE-02428-04 Synthesis of noncariogenic sweeteners (mice)

** R01DE-03993-07 Effect of saliva on the metabolism of dental plaque

R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism

R01DE-04903-03 Trace metal uptake in cariogenic streptococcus mutants

METAL CHELATES

SEE METAL COMPLEXES

METAL COMPLEXES

R01DE-04835-03 Anti-caries mechanism of fluoride complexes in vitro (human)

METAL COMPLEXES, LIGANDS

R01DE-05467-02 Pathogenesis of localized bone destruction

R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

** R01DE-05773-01 Ligand receptor interactions of cariogenic bacteria

METAL DISORDERS AND IMBALANCES

SEE ALSO CALCIUM (MINERAL) IMBALANCES

P01DE-01850-18 0068 Nutritional sources and metabolic roles of fluoride - Radioimmunoassay of parathyroid hormone in the rat

R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)

R23DE-05037-03 Biochemical role of zinc in teeth and bones

METAL METABOLISM

SEE ALSO IRON METABOLISM

R01DE-04615-04 Fluoride-cadmium interaction in dental caries (rats, human)

R23DE-05037-03 Biochemical role of zinc in teeth and bones

METAL METABOLISM DISORDERS

SEE METAL DISORDERS AND IMBALANCES

METAL OXIDES

SEE ALSO METALS, ALUMINUM (COMPOUNDS), ALUMINUM OXIDE

R01DE-04252-07 Semi and nonprecious metal-porcelain systems

R01DE-05460-02 Bonding of dental porcelain to non-precious alloys

METALLOPROTEINS, LACTOFERRIN

R01DE-01554-20 Host factors in caries resistance (human, rats)

R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)

R01DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins

R01DE-05531-03 Salivary immune factors (human, bacteria)

R01DE-05652-01 Biological role of lysozyme in human saliva

** R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)

METALLOPROTEINS, TRANSFERRIN

P50DE-02670-15 0035 Institute of Dental Research - Granulocyte growth and division

R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

METALS

SEE ALSO DENTAL MATERIALS, DENTAL METALS

R01DE-04903-03 Trace metal uptake in cariogenic streptococcus mutants

METALS, ALKALI METALS, LITHIUM

R23DE-05809-01 Effects of fluoride on physiology of oral bacteria

** N01DE-72409-08 Effect of strontium, lithium and fluorine on dental plaque (rats, human)

METALS, ALKALINE EARTH METALS, BARIUM (COMPOUNDS)

R01DE-05510-02 Physico-chemistry of strontium in caries lesions

METALS, ALKALINE EARTH METALS, MAGNESIUM

P01DE-01850-18 0068 Nutritional sources and metabolic roles of fluoride - Radioimmunoassay of parathyroid hormone in the rat

P01DE-01850-18 0084 Nutritional sources and metabolic roles of fluoride - Enamel, dentin and cementum in osteogenesis imperfecta (human)

P50DE-02668-15 0088 Regional dental research center - Hypervitaminosis D in lactation

R01DE-05510-02 Physico-chemistry of strontium in caries lesions

R23DE-05628-02 Influence of trace metals on dental health (rat)

R23DE-05809-01 Effects of fluoride on physiology of oral bacteria

R01DE-06113-01 Determinants of fluoride in the oral environment (Dogs, rats)

N01DE-12430-00 Investigation of anticaries vaccine in primates

METALS, ALKALINE EARTH METALS, STRONTIUM (COMPOUNDS)

R01DE-01830-19 Quantitation of enamel demineralization mechanisms

R01DE-01912-18 Tooth enamel apatite at the atomic level (human)

P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel

** R01DE-05510-02 Physico-chemistry of strontium in caries lesions

R23DE-05809-01 Effects of fluoride on physiology of oral bacteria

** N01DE-72409-08 Effect of strontium, lithium and fluorine on dental plaque (rats, human)

METALS, ALLOYS

SEE ALSO DENTAL MATERIALS, AMALGAM DENTAL

R01DE-02320-16 Clinical behavior of dental restorative materials

R01DE-03601-09 Localized corrosion of dental amalgam

** R01DE-03965-08 Dental alloy with small additions of other materials

** R01DE-04101-07 Corrosion of precious metal alloys (human)

** R01DE-04252-07 Semi and nonprecious metal-porcelain systems

** R01DE-04262-07 Amalgamation kinetics on Ag-Sn (X) alloys

R01DE-04516-03 Corrosion and clinical behavior of dental amalgam

** R01DE-04883-04 Nature of alloy systems for crown and bridge restorations (human)

** R23DE-05314-03 Dental alloy corrosion research

** R01DE-05321-02 Titanium alloys in dentistry

** R01DE-05441-02 Optimization of metal-ceramic restoration design

** R01DE-05460-02 Bonding of dental porcelain to non-precious alloys

** R23DE-05519-02 Oxidation behavior of Ni-base crown and bridge alloys

METALS, ALUMINUM (COMPOUNDS)

P50DE-02670-15 0020 Institute of Dental Research - Nutrition--Disease proneness during dental development

P50DE-02670-15 0036 Institute of Dental Research - Varnish and trace elements effects on enamel fluoride and dental caries (rats)

R01DE-04252-07 Semi and nonprecious metal-porcelain systems

METALS, ALUMINUM (COMPOUNDS), ALUMINUM OXIDE

R01DE-05353-04 Dental porcelains improvement with inorganic polymers

METALS, DIETARY

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY TRACE ELEMENTS AND MINERALS

METALS, HEAVY METALS, CADMIUM (COMPOUNDS)

P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel

(cont'd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level

**Oriented significantly to above subject

M Grant has subprojects describing specific research aspects

See Appendix for investigator's name and Grant Number

- R01DE-03856-07 (rats) Fluoride-selenium interaction in dental caries
- ** R01DE-04615-04 (rats, human) Fluoride-cadmium interaction in dental caries
- ** R01DE-04616-04 (rats) Fluoride-cadmium interaction in dental caries
- R23DE-05628-02 (rat) Influence of trace metals on dental health

METALS, HEAVY METALS, CHROMIUM (COMPOUNDS)

- R01DE-04252-07 systems Semi and nonprecious metal-porcelain systems
- R01DE-04883-04 bridge restorations (human) Nature of alloy systems for crown and
- R01DE-05321-02 Titanium alloys in dentistry
- R01DE-05441-02 Optimization of metal-ceramic restoration design
- R01DE-05460-02 Bonding of dental porcelain to non-precious alloys

METALS, HEAVY METALS, COBALT (COMPOUNDS)

- R01DE-04252-07 systems Semi and nonprecious metal-porcelain systems

METALS, HEAVY METALS, COPPER (COMPOUNDS)

- P50DE-02668-15 0191 Regional dental research center - Clinical evaluation of restorative materials and techniques
- ** R01DE-04262-07 Amalgamation kinetics on Ag-Sn (X) alloys
- R01DE-04704-05 X-ray and sem analysis of Cu rich dental amalgam
- R01DE-04883-04 bridge restorations (human) Nature of alloy systems for crown and
- R23DE-05314-03 Dental alloy corrosion research
- R23DE-05628-02 Influence of trace metals on dental health (rat)
- R01DE-06112-01 Filled sealant as a conservative restorative material (human)

METALS, HEAVY METALS, GOLD (COMPOUNDS)

- R01DE-02320-16 materials Clinical behavior of dental restorative materials
- R01DE-04101-07 Corrosion of precious metal alloys (human)
- R01DE-04883-04 bridge restorations (human) Nature of alloy systems for crown and
- R23DE-05314-03 Dental alloy corrosion research
- R01DE-05441-02 Optimization of metal-ceramic restoration design

METALS, HEAVY METALS, INDIUM (COMPOUNDS)

- R01DE-04883-04 bridge restorations (human) Nature of alloy systems for crown and
- R23DE-05314-03 Dental alloy corrosion research

METALS, HEAVY METALS, MANGANESE (COMPOUNDS)

- R01DE-04883-04 bridge restorations (human) Nature of alloy systems for crown and
- R23DE-05628-02 Influence of trace metals on dental health (rat)

METALS, HEAVY METALS, MERCURY (COMPOUNDS)

- SEE ALSO DENTAL MATERIALS, AMALGAM DENTAL
- R01DE-04262-07 Amalgamation kinetics on Ag-Sn (X) alloys

METALS, HEAVY METALS, MOLYBDENUM (COMPOUNDS)

- P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel
- R01DE-04252-07 Semi and nonprecious metal-porcelain systems
- R01DE-05510-02 Physico-chemistry of strontium in caries lesions

METALS, HEAVY METALS, NICKEL (COMPOUNDS)

- R01DE-04252-07 systems Semi and nonprecious metal-porcelain systems
- R01DE-04883-04 bridge restorations (human) Nature of alloy systems for crown and
- R01DE-05441-02 Optimization of metal-ceramic restoration design
- R01DE-05460-02 Bonding of dental porcelain to non-precious alloys
- ** R23DE-05519-02 Oxidation behavior of Ni-base crown and bridge alloys

METALS, HEAVY METALS, PALLADIUM (COMPOUNDS)

- R01DE-04101-07 Corrosion of precious metal alloys (human)
- R01DE-04252-07 Semi and nonprecious metal-porcelain systems
- R01DE-04883-04 bridge restorations (human) Nature of alloy systems for crown and
- R23DE-05314-03 Dental alloy corrosion research
- R01DE-05441-02 Optimization of metal-ceramic restoration design

METALS, HEAVY METALS, PLATINUM (COMPOUNDS)

- R01DE-04101-07 Corrosion of precious metal alloys (human)

METALS, HEAVY METALS, SILVER (COMPOUNDS)

- P50DE-02668-15 0191 Regional dental research center - Clinical evaluation of restorative materials and techniques
- R01DE-03965-08 Dental alloy with small additions of other materials
- R01DE-04252-07 systems Semi and nonprecious metal-porcelain systems
- R01DE-04262-07 Amalgamation kinetics on Ag-Sn (X) alloys
- R01DE-04883-04 bridge restorations (human) Nature of alloy systems for crown and
- R23DE-05314-03 Dental alloy corrosion research
- R01DE-05441-02 Optimization of metal-ceramic restoration design
- R23DE-05809-01 Effects of fluoride on physiology of oral bacteria

METALS, HEAVY METALS, TIN (COMPOUNDS)

- R01DE-03965-08 materials Dental alloy with small additions of other materials
- R01DE-04262-07 Amalgamation kinetics on Ag-Sn (X) alloys
- R01DE-04883-04 bridge restorations (human) Nature of alloy systems for crown and
- R23DE-05314-03 Dental alloy corrosion research
- R23DE-05809-01 Effects of fluoride on physiology of oral bacteria

METALS, HEAVY METALS, TITANIUM (COMPOUNDS)

- P50DE-02670-15 0036 Institute of Dental Research - Varnish and trace elements effects on enamel fluoride and dental caries (rats)
- R01DE-03497-09 Artificial tooth roots (Rhesus monkeys, human)
- R01DE-04414-06 Porous high density polyethylene tooth roots (monkeys)
- ** R01DE-04705-03 Reactions of titanium fluoride with hydroxyapatite
- R01DE-04835-03 Anti-carries mechanism of fluoride complexes in vitro (human)
- R23DE-05314-03 Dental alloy corrosion research
- ** R01DE-05321-02 Titanium alloys in dentistry
- R01DE-05563-02 The blade implant--Clinical efficacy and safety (human)

METALS, HEAVY METALS VANADIUM (COMPOUNDS)

- P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel

METALS, HEAVY METALS, ZINC (COMPOUNDS)

- P50DE-02670-15 0020 Institute of Dental Research - Nutrition--Disease proneness during dental development
- R01DE-03965-08 Dental alloy with small additions of other materials
- R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)
- ** R23DE-05037-03 Biochemical role of zinc in teeth and bones
- R23DE-05628-02 Influence of trace metals on dental health (rat)
- R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
- ** R01DE-05999-01 The role of nutrition in oral health

METALS, METALLOIDS, SELENIUM (COMPOUNDS)

- P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel
- ** R01DE-03856-07 Fluoride-selenium interaction in dental caries (rats)
- R23DE-05628-02 Influence of trace metals on dental health (rat)

METALS, RARE EARTHS, ZIRCONIUM (COMPOUNDS)

- R01DE-04835-03 Anti-carries mechanism of fluoride complexes in vitro (human)
- R01DE-05353-04 Dental porcelains improvement with inorganic polymers

METALS CARCINOGENESIS

- SEE NEOPLASTIC TRANSFORMATION, CARCINOGENS, CHEMICAL

METALS POISONING

- R01DE-04615-04 Fluoride-cadmium interaction in dental caries (rats, human)
- R01DE-04616-04 Fluoride-cadmium interaction in dental caries (rats)
- R23DE-05628-02 Influence of trace metals on dental health (rat)

METALS POISONING, LEAD POISONING

- P50DE-02670-15 0035 Institute of Dental Research - Granulocyte growth and division
- R23DE-05628-02 Influence of trace metals on dental health (rat)

METASTASIS

- SEE NEOPLASTIC GROWTH, NEOPLASMS METASTASIS

METHACRYLATES

- SEE PLASTICS, ACRYLIC POLYMERS, METHACRYLATES

METHOTREXATE

- SEE FOLIC ACID ANTAGONISTS, METHOTREXATE

METHYL TRANSFER

- SEE ALKYL TRANSFER, TRANSMETHYLATION

METHYLUREA

- SEE AMIDES, UREA

METRONIDAZOLE

- SEE IMIDAZOLES, METRONIDAZOLE

MG

- SEE METALS, ALKALINE EARTH METALS, MAGNESIUM

MHC (LOCUS)

- SEE IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)

MICE (LABORATORY)

- SEE MAMMALS, RODENTS, MYDMORPHA, MICE (LABORATORY)*

MICROBIAL ANTIGENS

- SEE IMMUNOLOGY, ANTIGENS MICROBIAL

MICROBIAL CULTURE

- SEE GROWTH MICROORGANISMS, MICROBIAL CULTURE

MICROBIAL GENETICS

- SEE GENETICS, MICROBIAL

MICROBIAL GROWTH

- SEE GROWTH MICROORGANISMS

MICROBIAL IDENTIFICATION AND CLASSIFICATION (TECHNIQUES)

- P50DE-02600-15 0037 Support for oral biology research center - Periodontal microflora (human)
- P01DE-02847-13 0022 Microbial ecology and its relation to dental disease - Cemental caries as a dental problem (human, rats, primates)
- P01DE-02847-13 0023 Microbial ecology and its relation to dental disease - Microbiota associated with periodontal diseases (human, rats, hamsters)
- ** R01DE-03488-10 Microbial composition of developing dental plaque
- ** R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- ** R01DE-05054-03 Periodontal diseases--Microbiological studies
- ** R01DE-05104-02 Periodontitis--Microbial etiology and prediction
- ** P50DE-05139-04 0001 Clinical research center for periodontal disease - Microbiology
- ** R01DE-05144-03 Periodontal disease--Role of spirochetes (rabbits, human)
- ** R01DE-05156-03 Immunoidentification of periodontal plaque bacteria
- ** R01DE-05218-03 DNA homologies among bacteria of periodontal diseases
- ** R01DE-05560-01 Rapid identification of oral bacteria
- N01DE-72408-06 Cross-reacting antigens/oral flora acidogenic bacteria
- ** N01DE-92418-05 Characterize and identify pleomorphic oral bacteria

MICROBIAL IDENTIFICATION AND CLASSIFICATION, SEROTYPING

- SEE ALSO IMMUNITY, CROSS IMMUNITY
- ** P50DE-02600-15 0035 Support for oral biology research center - Serotyping of microbes for diagnosis of periodontitis (rabbits)
- R01DE-03180-11 Microbiologic studies of the human oral streptococci
- R01DE-05591-01 Mechanisms of virulence of oral periodontopathogens

MICROBIAL IMMUNOLOGY

- SEE IMMUNOLOGY, MICROBIAL

MICROBIAL INTERACTION

- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

MICROBIAL MATTS

- R01DE-04926-04 dental plaque Bacterial coaggregation mechanisms in
- R01DE-05104-02 Periodontitis--Microbial etiology and prediction
- R01DE-05334-02 Periodontal therapy by controlled local drug delivery (human)
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

MICROBIAL ORAL FLORA

- SEE ALSO BACTERIA, ACTINOMYCETALES, ACTINOMYCES*
- SEE ALSO BACTERIA, ACTINOMYCETALES, LEPTOTRICHIA*
- SEE ALSO BACTERIA, ACTINOMYCETALES, ROTHIA DENTOCARIOSA
- SEE ALSO BACTERIA, BACTEROIDACEAE, BACTEROIDES*
- SEE ALSO BACTERIA, BACTEROIDACEAE, BACTEROIDES MELANINGENICUS*
- SEE ALSO BACTERIA, BACTEROIDACEAE, FUSOBACTERIA*
- SEE ALSO BACTERIA, CORYNEFORM GROUP, CORYNEBACTERIUM*
- SEE ALSO BACTERIA, NEISSERIAE, NEISSERIA*
- SEE ALSO BACTERIA, NEISSERIAE, VEILLONELLA*
- SEE ALSO BACTERIA, PSEUDOMONADALES, VIBRIO*
- SEE ALSO BACTERIA, SPIROCHETES, TREPONEMA*
- SEE ALSO BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS*

(contd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects
See Appendix for investigator's name and Grant Number.

- SEE ALSO BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS MITIS*
- SEE ALSO BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS MUTANS*
- SEE ALSO BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS SALIVARIUS*
- SEE ALSO DENTISTRY
- R01DE-01554-20 Host factors in caries resistance (human, rats)
- P50DE-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
- P50DE-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
- ** P50DE-02600-15 0035 Support for oral biology research center - Serotyping of microbes for diagnosis of periodontitis (rabbits)
- ** P50DE-02600-15 0037 Support for oral biology research center - Periodontal microflora (human)
- ** P50DE-02600-15 0039 Support for oral biology research center - Saliva in abnormal bacterial adherence and colonization (human)
- P50DE-02600-15 0040 Support for oral biology research center - Fate of actinomyces viscosus components within phagocytic cells
- P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)
- ** P50DE-02623-14 0005 Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- ** P50DE-02623-14 0009 Center for oral health research - Oral microorganisms in periodontal health and disease (human, rats)
- P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction
- ** P50DE-02623-14 0014 Center for oral health research - Surface receptors on plaque forming organisms
- ** P50DE-02623-14 0023 Center for oral health research - Interactions of oral bacteria and polymorphonuclear leukocytes
- ** P50DE-02623-14 0032 Center for oral health research - Interactions of salivary agglutinins and oral bacteria
- P50DE-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions
- P50DE-02670-15 0018 Institute of Dental Research - Structure of human secretory immunoglobulin A
- ** P50DE-02670-15 0025 Institute of Dental Research - Biochemical basis for the cariogenic property of Streptococcus mutans (rat)
- ** P50DE-02670-15 0033 Institute of Dental Research - Genetic and biochemical basis for S mutans virulence (rats)
- P50DE-02731-15 0021 Development support for dental research institute - Bacterial specificity in periodontal disease
- P50DE-02731-15 0033 Development support for dental research institute - Clinical trials of periodontal therapy
- P50DE-02731-15 0035 Development support for dental research institute - Immune regulation in periodontal disease
- M P01DE-02847-13 Microbial ecology and its relation to dental disease
- ** P01DE-02847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
- ** P01DE-02847-13 0021 Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)
- ** P01DE-02847-13 0022 Microbial ecology and its relation to dental disease - Cemental caries as a dental problem (human, rats, primates)
- ** P01DE-02847-13 0023 Microbial ecology and its relation to dental disease - Microbiota associated with periodontal diseases (human, rats, hamsters)
- ** R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)
- ** R01DE-03118-11 Inhibition of saccharide metabolism by oral flora
- ** R01DE-03180-11 Microbiologic studies of the human oral streptococci
- R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)
- ** R01DE-03487-10 Inhibition of human cariogenic streptococci
- R01DE-03488-10 Microbial composition of developing dental plaque
- ** R01DE-03654-09 Molecular basis of dental caries (human)
- R01DE-03713-06 Effect of fissure sealant on progress of dental caries (human)
- ** R01DE-03731-06 Dextran sucrose of Streptococcus sanguis
- R01DE-03739-09 Glycosyltransferases from oral bacteria (bacteria)
- R01DE-03758-07 Virulence characterization and immunization against S mutans (rats, rabbits)
- R01DE-03993-07 Effect of saliva on the metabolism of dental plaque
- R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)
- ** R01DE-04061-07 Salivary antibodies to S mutans-Induction and effects (monkeys)
- ** R01DE-04174-07 Variations in the surface structures of oral bacteria
- ** R01DE-04175-07 Variations in the surface structures of oral bacteria
- R01DE-04217-07 Effective immunity to dental caries-Cellular basis
- ** R01DE-04224-07 Genetics of oral microflora
- ** R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)
- R01DE-04278-06 Human saliva-streptococcal metabolic interactions
- R01DE-04296-07 Lysozyme-Cell surface interactions and oral defense
- R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
- R01DE-04385-06 Mechanism of dental caries (human)
- R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
- R01DE-04486-04 Kinetics and mechanisms of action of fluorides
- R01DE-04504-03 Plaque bacteria as predictors of human dental caries
- ** R01DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins
- ** R01DE-04529-05 Replacement therapy of dental caries (rats, monkeys)
- R01DE-04614-05 Adherence of oral streptococci to hydroxyapatite
- ** R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- R01DE-04744-04 New antimicrobial agents for preventing oral diseases
- ** R01DE-04795-05 Characteristics of cariogenic dental plaque
- P50DE-04881-05 0001 Center for clinical research in periodontal diseases - Diagnosis and treatment of destructive periodontal diseases
- ** P50DE-04881-05 0002 Center for clinical research in periodontal diseases - Relationship of subgingival microbiota to the etiology of periodontal diseases
- ** P50DE-04881-05 0003 Center for clinical research in periodontal diseases - Host immunologic response to oral microorganisms
- P50DE-04881-05 0004 Center for clinical research in periodontal diseases - Relation of inflammation mediators to destructive periodontal diseases
- M P50DE-04898-05 Periodontal disease research center
- ** P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
- ** P50DE-04898-05 0002 Periodontal disease research center - Host response in periodontal disease (human)
- ** P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
- ** R01DE-04903-03 Trace metal uptake in cariogenic streptococcus mutans
- ** R01DE-04926-04 Dental plaque
- ** R01DE-04957-03 Bacterial metabolites in oral diseases
- R01DE-05017-03 Characterization of surface antigens of S mutans
- ** R01DE-05027-04 Binding of fluoride by cariogenic bacteria
- R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
- R23DE-05050-02 Sources of toxins from human dental plaque
- ** R01DE-05054-03 Periodontal diseases--Microbiological studies
- ** R01DE-05104-02 Periodontitis--Microbial etiology and prediction
- ** R01DE-05123-04 Periodontopathic bacteria-chemical-biologic nature (mammals)
- ** P50DE-05139-04 0001 Clinical research center for periodontal disease - Microbiology
- ** P50DE-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations
- P50DE-05139-04 0003 Clinical research center for periodontal disease
- ** R01DE-05141-03 Cariogenic mechanisms of gingival plaque bacteria
- R01DE-05144-03 Periodontal disease--Role of spirochetes (rabbits, human)
- R01DE-05156-03 Immunoidentification of periodontal plaque bacteria
- ** R01DE-05180-03 Composition of S mutans in different growth environments
- R01DE-05218-03 DNA homologies among bacteria of periodontal diseases
- R01DE-05224-01 Enamel silylation as a caries prevention method (human, animals)
- R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)
- ** R01DE-05252-01 Bidirectional effects of subgingival dental plaque
- ** R23DE-05331-01 Local host mechanism in periodontal disease (human, monkeys)
- R01DE-05334-02 Periodontal therapy by controlled local drug delivery (human)
- R01DE-05352-03 Immunochemical studies in periodontal disease
- ** R01DE-05427-01 Adherence mechanisms of oral microbes
- ** R23DE-05429-03 Adherence of periodontal disease-associated bacteria
- R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence
- R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)
- ** R01DE-05462-01 Saliva mediated aggregation of oral bacteria (human)
- R01DE-05476-02 Novel peptide derived sweeteners
- R01DE-05494-02 Activation of macrophages in periodontal disease
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- R01DE-05512-02 Role of macrophages in periodontal disease
- R01DE-05525-02 Nature of the permeability barrier in oral epithelium
- R01DE-05531-03 Salivary immune factors (human, bacteria)
- ** R01DE-05560-01 Rapid identification of oral bacteria
- ** R23DE-05599-02 Microbiology of ligature-induced periodontitis
- R01DE-05606-02 Pili of S sanguis and their role in adhesion (human, rabbits)
- R01DE-05626-01 Role of complement in periodontal disease
- ** R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)
- ** R01DE-05640-01 Cytotoxicity of periodontopathic bacteria
- R01DE-05652-01 Biological role of lysozyme in human saliva
- R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)
- ** R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
- R01DE-05732-02 Specificity of cell mediated immune response in periodontal disease
- R23DE-05749-01 Salivary proline-rich proteins--Localization/secretion (monkeys)
- ** R13DE-05753-01 Symposium on host-bacteria in periodontal diseases
- ** R01DE-05773-01 Ligand receptor interactions of cariogenic bacteria (goats, rabbits, human)
- R23DE-05777-01 Cationic protein in submandibular saliva
- ** R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
- R01DE-05817-01 Gingival collagenase--Quantitation and localization (rabbits, mice, human)
- ** R23DE-05887-01 Effects of oral bacteria on epithelium in vitro
- ** R23DE-05942-01 Airway factors in cleft palate dentofacial deformity
- ** R23DE-05951-01 Selective microbial ecology of periodontosis siblings
- R23DE-05967-01 Role of prostaglandin E in periodontal disease activity
- ** R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens
- ** R01DE-06070-01 Antibiotic susceptibilities of periodontal bacteria
- N01DE-12430-00 Investigation of anticaries vaccine in primates
- N01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)
- N01DE-12434-00 Identify cariogenic elements of food
- ** N01DE-72408-06 Cross-reacting antigens/oral flora acidogenic bacteria
- N01DE-72409-08 Effect of strontium, lithium and fluorine on dental plaque (rats, human)
- ** N01DE-92418-05 Characterize and identify pleomorphic oral bacteria

MICROBIAL PHYSIOLOGY STUDY SECTION

- ** R01DE-03118-11 Inhibition of saccharide metabolism by oral flora
- ** R01DE-04224-07 Genetics of oral microflora
- ** R01DE-04957-03 Bacterial metabolites in oral diseases
- ** R01DE-05102-04 Potential anti-caries agents (rats)
- ** R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)

MICROBIAL POPULATION STUDIES

SEE POPULATION STUDIES MICROORGANISMS

MICROBIAL REPRODUCTION

SEE REPRODUCTION MICROORGANISMS

MICROBIAL RESISTANCE TO DRUGS

SEE DRUGS RESISTANCE, MICROBIAL

MICROCIRCULATION

SEE CARDIOVASCULAR SYSTEM, MICROCIRCULATION

MICROFILAMENTS

SEE CELL COMPONENTS, MICROFILAMENTS

MICROORGANISMS, ANAEROBES

SEE ALSO BACTERIA, NEISSERIAEAE, VEILLONELLA*

- P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)
- ** R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- ** R01DE-04808-02 Virulence factors of gram negative corroding bacteria
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

MICROORGANISMS VIRULENCE

SEE ALSO DRUGS RESISTANCE, MICROBIAL

- P50DE-02623-14 0005 Center for oral health research - Mechanisms of pathogenicity in two groups of periodontopathic bacteria
- ** P50DE-02670-15 0033 Institute of Dental Research - Genetic and biochemical basis for S mutans virulence (rats)
- P01DE-02847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects. See Appendix for investigator's name and Grant Number.

(contd.)

- P01DE-02847-13 0022 Microbial ecology and its relation to dental disease - Cemental caries as a dental problem (human, rats, primates)
- P01DE-02847-13 0023 Microbial ecology and its relation to dental disease - Microbiota associated with periodontal diseases (human, rats, hamsters)
- ** R01DE-03758-07 Virulence characterization and immunization against *S* mutants (rats, rabbits)
- R01DE-04217-07 Effective immunity to dental caries-Cellular basis
- R01DE-04224-07 Genetics of oral microflora
- R01DE-04645-04 A genetic-biochemical analysis of spirochete motility
- ** R01DE-04808-02 Virulence factors of gram negative corroding bacteria
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- ** R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens

MICROSURGERY AND MICRODISSECTION

SEE SURGERY, MICROSURGERY AND MICRODISSECTION

MICROTUBULES

SEE CELL COMPONENTS, MICROTUBULES (GENERAL)

MIDBRAIN

SEE BRAIN, MESENCEPHALON

MIDCHILDHOOD

SEE CHILDREN, MIDCHILDHOOD (6 TO 12 YRS)

MIDDLE AGE

SEE AGE (HUMAN), ADULT, MIDDLE AGE (45 TO 64 YRS)

MIDDLE EAR DISORDERS

SEE EAR DISORDERS, MIDDLE EAR DISORDERS

MIF (LYMPHOKINES)

SEE HYPERSENSITIVITY, LYMPHOKINES, MIGRATION INHIBITORY FACTOR

MIGRATION, CELL

SEE CELL MIGRATION

MIGRATION INHIBITORY FACTOR

SEE HYPERSENSITIVITY, LYMPHOKINES, MIGRATION INHIBITORY FACTOR

MILK

SEE BODY FLUIDS, MILK

MINERAL BALANCE - METABOLISM

SEE CALCIUM (MINERAL) BALANCE (METABOLISM)

MINERAL METABOLISM DISORDERS

SEE CALCIUM (MINERAL) IMBALANCES

MINERALIZATION ENHANCING DRUGS

SEE CALCIFICATION ENHANCING DRUGS (CALCIUM POSITIVE BALANCE DRUGS)

MINERALIZATION INHIBITORS

SEE CALCIFICATION INHIBITORS (CALCIUM NEGATIVE BALANCE DRUGS)

MINERALIZATION OF BONE

SEE SKELETAL SYSTEM, BONE DEVELOPMENT, OSSIFICATION NORMAL

MINERALS

SEE CHEMICALS (GENERAL), MINERALS (GENERAL)

MINERALS, DIETARY

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY TRACE ELEMENTS AND MINERALS

MITOCHONDRIA

SEE CELL COMPONENTS, MITOCHONDRIA

MITOGENIC FACTORS, PLANT

SEE PLANTS PROTEINS, LECTINS

MITOGENS

SEE ALSO PLANTS EXTRACTS, POKEWEED EXTRACTS

SEE ALSO PLANTS PROTEINS, LECTINS

P50DE-02623-14 0033 Center for oral health research -

Immune system in regulation of angiogenesis

R01DE-05467-02 Pathogenesis of localized bone obstruction

MITOSIS

SEE CELL DIVISION, MITOSIS

MIXED LEUKOCYTE REACTION GENES

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

MN

SEE METALS, HEAVY METALS, MANGANESE (COMPOUNDS)

MO

SEE METALS, HEAVY METALS, MOLYBDENUM (COMPOUNDS)

MODELS (GENERAL)

SEE ALSO COMPUTER SIMULATION

SEE ALSO ENZYME MODELS

** R01DE-04645-04 A genetic-biochemical analysis of spirochete motility

MODELS, BIOLOGICAL

** P01DE-01697-19 0035 A research program in craniofacial problems - Non-human primate model of cleft palate (monkeys)

** P01DE-01697-19 0040 A research program in craniofacial problems - Pattern recognition for reconstruction of nasal capsular anatomy

P01DE-01850-18 0081 Nutritional sources and metabolic

roles of fluoride - Effect of fluoride intake on strain N mice

P01DE-01850-18 0085 Nutritional sources and metabolic

roles of fluoride - Absorption of fluoride from dietary

substances (rats)

P01DE-01850-18 0086 Nutritional sources and metabolic

roles of fluoride - Effect of fluoride intake on serum alkaline

phosphatase activity (mice)

R01DE-02212-13 Circulation in teeth and supporting

structures (dogs, monkeys)

P50DE-02623-14 0013 Center for oral health research -

Mechanisms of secretory antibody induction

P50DE-02668-15 0172 Regional dental research center -

Genetic and environmental factors interaction in development

of cleft lip (mice)

P50DE-02670-15 0020 Institute of Dental Research -

Nutrition-Disease proneness during dental development

P50DE-02670-15 0033 Institute of Dental Research - Genetic

and biochemical basis for *S* mutants virulence (rats)

P50DE-02731-15 0032 Development support for dental

research institute - Epithelial cell basal lamina biosynthesis

(rats)

P50DE-02731-15 0038 Development support for dental

research institute - Antiviral chemotherapy-Drug delivery

component

P01DE-02847-13 0022 Microbial ecology and its relation to

dental disease - Cemental caries as a dental problem (human,

rats, primates)

P01DE-02848-11 0002 Biology of connective tissue, bones,

and teeth - Steroid receptors in craniofacial teratology (mice)

R01DE-03318-10 The molecular nature of gingival and

mucosal collagen

R01DE-04660-06 Keratohyalin in keratinization-Oral mucosa

and skin (human)

R01DE-04795-05 Characteristics of cariogenic dental plaque

Temporalis flaps in the treatment of facial

paralysis (monkeys)

R01DE-04926-04 Bacterial coaggregation mechanisms in

dental plaque

R23DE-05037-03 Biochemical role of zinc in teeth and bones

Adjustive cranial skeletal growth (rats)

R01DE-05145-03 Neuroeffector transmission in a simple

salivary gland (snails, mice)

R01DE-05352-03 Immunochemical studies in periodontal

disease

R01DE-05354-04 Prevention of dental caries (rats, human)

R23DE-05418-03 In vivo forces on endosseous dental implants

(dogs)

R01DE-05459-02 Phenytoin-Pathogenesis of gingival

overgrowth (cats)

R23DE-05592-02 Biochemical mechanism of steroid-induced

clefting (mice)

R01DE-05616-03 Matrix-cell interaction in craniofacial

development (chick embryos)

R23DE-05627-02 Effects of mechanical forces on craniofacial

growth (monkeys, rabbits)

R01DE-05678-02 Salivary changes after cancer

chemotherapeutic drugs

P01DE-05837-01 0004 Growth, surgical, and speech aspects

of cleft palate - Surgery (human, animals)

R01DE-05937-01 Proteolipids and mineralization of bones and

teeth (bacteria, rabbits)

MODELS, CHEMICAL

SEE ALSO ENZYME MODELS

R01DE-01830-19 Quantitation of enamel demineralization

mechanisms

P50DE-02668-15 0176 Regional dental research center -

Collagen biochemistry and the myeloblastosis associated virus

infected cells

R01DE-04600-04 Hydroxyapatite remineralization-Role of

fluoride

MODELS, MATHEMATICAL

SEE ALSO COMPUTER SIMULATION

P01DE-01697-19 0040 A research program in craniofacial

problems - Pattern recognition for reconstruction of nasal

capsular anatomy

R01DE-01830-19 Quantitation of enamel demineralization

mechanisms

P50DE-02668-15 0150 Regional dental research center -

Polymerization of tooth restorative composite materials

P01DE-02872-12 0034 Craniofacial dysmorphology -

Digitization of roentgencephalometric data (human)

** R01DE-03545-09 Prediction of tooth displacement (human)

R01DE-03953-07 Force systems from orthodontic appliances

R01DE-04047-05 Extensibility characteristics of human cheek

Hydroxyapatite remineralization-Role of

fluoride

R01DE-04610-03 Physiological studies on mastication

(human)

R01DE-05136-03 Osteoclast origin and histogenesis in

periodontium (rats)

R01DE-05180-03 Composition of *S* mutants in different growth

environments

R01DE-05292-03 Biological prosthetic attachment (dog)

R01DE-05423-02 Diffuse reflectance by esthetic dental

materials

R01DE-05582-01 Computer graphic analysis of cranio-facial

morphology

MOLECULAR BIOLOGY (GENERAL)

** R01DE-01912-18 Tooth enamel apatite at the atomic level

(human)

P50DE-02623-14 0026 Center for oral health research -

Collagen biosynthesis in the periodontium

** P50DE-02623-14 0032 Center for oral health research -

Interactions of salivary agglutinins and oral bacteria

** P50DE-02668-15 0196 Regional dental research center -

Cytochemical demonstration of macromolecules of craniofacial

tissue

** P50DE-02670-15 0019 Institute of Dental Research -

Chemistry and molecular biology of the connective tissue

protein, collagen

P50DE-02670-15 0025 Institute of Dental Research -

Biochemical basis for the cariogenic property of *Streptococcus*

mutans (rat)

P50DE-02670-15 0029 Institute of Dental Research -

Structure of connective tissue proteoglycans (cattle)

P01DE-02848-11 0001 Biology of connective tissue, bones,

and teeth - Mesenchymal interactions (mice, rabbit)

R01DE-04844-04 Stress-related bone resorption-Mechanisms

of action (rats)

R01DE-04926-04 Bacterial coaggregation mechanisms in

dental plaque

R01DE-04970-04 Molecular characterization of odontogenesis

by 5-bromodeoxyuridine

R01DE-05141-03 Cariogenic mechanisms of gingival plaque

bacteria

R23DE-05429-03 Adherence of periodontal disease-associated

bacteria

R23DE-05592-02 Biochemical mechanism of steroid-induced

clefting (mice)

R01DE-05666-01 Biochemistry of salivary lipids (monkeys,

rats, human)

R01DE-05732-02 Specificity of cell mediated immune response

in periodontal disease

MOLECULAR CONDENSATIONS, COPOLYMERS

R01DE-05327-03 Polymeric polyphosphonates on dental caries

and plaque (rats)

MOLECULAR CONDENSATIONS, POLYMERIZATION-DEPOLYMERIZATION

** P50DE-02668-15 0150 Regional dental research center -

Polymerization of tooth restorative composite materials

P50DE-02670-15 0018 Institute of Dental Research -

Structure of human secretory immunoglobulin A

R01DE-03578-10 Biosynthetic study of dental plaque

polysaccharides

MOLECULAR CONDENSATIONS, POLYMERS (GENERAL)

SEE ALSO MOLECULAR CONDENSATIONS, RESINS

** P50DE-02668-15 0149 Regional dental research center -

Strengths of polymers in tooth restorative materials

P50DE-02670-15 0024 Institute of Dental Research -

Metabolism of connective tissue proteoglycans

R01DE-03180-11 Microbiologic studies of the human oral

streptococci

R01DE-03487-10 Inhibition of human cariogenic streptococci

** R01DE-04814-02 New polymers for permanent soft denture

liners

R01DE-05327-03 Polymeric polyphosphonates on dental caries

and plaque (rats)

** R01DE-05353-04 Dental porcelains improvement with

inorganic polymers

** R01DE-05596-02 Topically-applied polymers for caries

prevention

** R01DE-05637-01 Mechanical properties of dental composite

materials

** R23DE-05945-01 Physicochemical modifications of dental

restoratives

MOLECULAR CONDENSATIONS, RESINS

R01DE-02320-16 Clinical behavior of dental restorative

materials

** P50DE-02668-15 0191 Regional dental research center -

Clinical evaluation of restorative materials and techniques

R01DE-03246-12 Biochemical mechanisms relevant to

dentistry (bacteria)

R01DE-05137-03 Microscopic and clinical study of cervical

erosion

R01DE-05354-04 Prevention of dental caries (rats, human)

MOLECULAR STRUCTURE

SEE CHEMICAL STRUCTURE

MOLECULAR STRUCTURE-BIOLOGICAL ACTIVITY

SEE CHEMICAL STRUCTURE-BIOLOGICAL ACTIVITY

MOLECULAR WEIGHT

R01DE-04844-04 Stress-related bone resorption-Mechanisms

- P50DE-02731-15 0031** Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues
- R01DE-03934-07** Differentiation of oral epithelium (rats)
- R23DE-05062-03** Tissue interactions during odontogenesis
- R01DE-05141-03** Cariogenic mechanisms of gingival plaque bacteria
- R01DE-05180-03** Composition of S mutants in different growth environments
- R01DE-05251-02** Salivary gland secretory mechanisms (rats)
- R23DE-05429-03** Adherence of periodontal disease-associated bacteria
- R01DE-05640-01** Cytotoxicity of periodontopathic bacteria
- R01DE-05678-02** Salivary changes after cancer chemotherapy
- R01DE-05722-02** Bactericidal activity of lactoferrin on oral flora
- MOLLUSKS, PELECYPODS***
- ** R01DE-05800-01** Formation and biochemical composition of sea mussel
- R23DE-05956-01** The adhesive of *Mytilus edulis*
- MOLYBDENUM (COMPOUNDS)**
SEE METALS, HEAVY METALS, MOLYBDENUM (COMPOUNDS)
- MONGOLISM**
SEE GENETIC DISORDERS, DOWN'S SYNDROME
- MONITORING DEVICES**
SEE BIOMEDICAL SYSTEMS AUTOMATED, MONITORING DEVICES
- MONOCYTES**
SEE BLOOD CELLS, MONOCYTES
- MONOSACCHARIDES**
SEE CARBOHYDRATES, MONOSACCHARIDES
- MORBIDITY STATISTICS**
SEE POPULATION STUDIES HUMAN, MORBIDITY
- MORPHINE RECEPTORS**
SEE NEUROTRANSMITTERS RECEPTORS, ENKEPHALIN RECEPTORS
- MORPHINES**
SEE ALKALOIDS, MORPHINES
- MORPHOGENESIS**
SEE GROWTH AND DEVELOPMENT, HISTOGENESIS
- MOSAICISM**
SEE TISSUE MOSAICISM
- MOTHER-CHILD INTERACTION**
SEE FAMILY, PARENT-OFFSPRING, MOTHER-CHILD INTERACTION
- MOTION IMAGES, SCANNING**
SEE RADIOGRAPHY, SCANNING, OSR
- MOTIVATION**
SEE PSYCHOLOGY, MOTIVATION
- MOTOR CORTEX**
SEE BRAIN, CEREBRAL CORTEX, MOTOR CORTEX
- MOTOR IMPULSES**
SEE PSYCHOMOTOR FUNCTION
- MOTOR NEURONS**
SEE NEUROMOTOR SYSTEM, MOTOR NEURONS
- MOUTH**
SEE ORAL-PHARYNGEAL, MOUTH
- MOUTH NEOPLASMS**
SEE NEOPLASMS OF ORAL-PHARYNGEAL STRUCTURES, MOUTH NEOPLASMS
- MOUTHWASHES**
SEE CONSUMER PRODUCTS, MOUTHWASHES
- MOVEMENT, BODY**
SEE SKELETAL MOVEMENT, BODY MOVEMENT
- MOVEMENT, EYE**
SEE EYE MOVEMENTS
- MOVEMENT PERCEPTION, BODY**
SEE SENSORY-PERCEPTUAL PROCESSES, PROPRIOCEPTION
- MPD SYNDROME**
SEE ORAL-PHARYNGEAL DISORDERS, MPD SYNDROME
- MRNA**
SEE NUCLEIC ACIDS, MRNA
- MS-B**
SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)
- MUCIN**
SEE PROTEOGLYCANS, MUCIN
- MUCINASE**
SEE CARBOHYDRASES, HYALURONIDASE
- MUCOIDS**
SEE PROTEOGLYCANS
- MUCOPEPTIDES**
SEE PEPTIDOGLYCANS
- MUCOPOLYSACCHARIDES**
SEE POLYSACCHARIDES, GLYCOSAMINOGLYCANS

MUCOPOLYSACCHARIDOSIS I

SEE METABOLIC DISORDERS INBORN,
MUCOPOLYSACCHARIDOSIS, LIPOCHONDRODYSSTROPHY

MUCOPROTEINS

SEE PROTEOGLYCANS

MUCOSA, ESOPHAGEAL

SEE ORAL-PHARYNGEAL, MUCOSA

MUCOSA, ORAL-PHARYNGEAL

SEE ORAL-PHARYNGEAL, MUCOSA

MUCOUS MEMBRANE

SEE MEMBRANE, MUCOUS MEMBRANE

MUCOVISCIDOSIS

SEE METABOLIC DISORDERS INBORN, CYSTIC FIBROSIS

MULTIPLE DRUG THERAPY

SEE DRUGS, CHEMOTHERAPY, DRUGS COMBINATION

MULTIPLE MYELOMA

SEE NEOPLASMS OF BLOOD AND RE SYSTEM, BONE MARROW
NEOPLASMS, MULTIPLE MYELOMA

MULTIPLE TREATMENT WITH DRUGS

SEE DOSAGE AND ROUTE, RATE AND DURATION OF
ADMINISTRATION

MUMPS

SEE VIRUS DISEASES, PARAMYXOVIRIOAE, MUMPS

MURAMIC ACID

SEE SUGAR ACIDS, MURAMIC ACID

MURAMIDASE

SEE CARBOHYDRASES, LYSOZYME

MUREIN

SEE PEPTIDOGLYCANS

MUSCARINIC AGENTS

SEE NEUROPHARMACOLOGICAL AGENTS,
PARASYMPATHOMIMETIC

MUSCARINIC RECEPTORS

SEE NEUROTRANSMITTERS RECEPTORS, CHOLINERGIC
RECEPTORS

MUSCLE CELLS, SARCOMERES

R01DE-04164-06 Functional properties of mammalian
masticatory muscles

MUSCLE CONTRACTION

SEE MUSCLE FUNCTION, MUSCLE CONTRACTION

MUSCLE FUNCTION

- P50DE-02668-15 0214** Regional dental research center -
- ** R01DE-04164-06** Functional properties of mammalian
masticatory muscles
- ** R01DE-04227-07** Adaptations to changes in masticatory
muscle length (monkeys)
- R23DE-05036-03** Nocturnal masseter muscle activity and jaw
dysfunction (human)
- ** R01DE-05112-03** Muscle activity and control in mastication
(mammals, lizards)
- ** R23DE-05232-03** Growth and function of the muscles of
mastication (monkeys)
- ** R01DE-05397-01** Craniofacial bone formation and muscle
activity (Rhesus monkey)

MUSCLE FUNCTION, ELECTROMYOGRAPHY*

**** P50DE-04898-05 0004** Periodontal disease research center -
Periodontal disease and the electromyographic silent period
(human)

MUSCLE FUNCTION, MUSCLE CONTRACTION

- SEE ALSO NEUROMOTOR SYSTEM, NEUROMUSCULAR
TRANSMISSION
- ** R23DE-05036-03** Nocturnal masseter muscle activity and jaw
dysfunction (human)
- R23DE-05232-03** Growth and function of the muscles of
mastication (monkeys)
- R01DE-05396-02** Craniofacial adaptations after maxillary
osteotomy (monkeys)
- ** R01DE-05495-02** Myofibroblast contraction in periodontium
(rats)
- ** R01DE-05558-01** Sensory alterations of craniofacial form
(Rhesus monkeys)
- MUSCLE FUNCTION, MUSCLE RELAXATION**
- R01DE-04494-05** Control of stress during dental procedures
(human)
- ** R01DE-04889-04** Dental significance of jaw muscle silent
periods (human)
- MUSCLE FUNCTION, MUSCLE STRETCH
(RECEPTORS)**
- R01DE-04884-13** Neural processes in somatic movement
(monkeys)

MUSCLE FUNCTION, MUSCLE STRETCH REFLEX

SEE ALSO SKELETAL MOVEMENT, POSTURE

**** R01DE-04047-05** Extensibility characteristics of human cheek

MUSCLE FUNCTION, MUSCLE TENSION

R01DE-04164-06 Functional properties of mammalian
masticatory muscles

MUSCLE PROTEINS (AND CONTRACTILE PROTEINS)

R01DE-05495-02 Myofibroblast contraction in periodontium
(rats)

MUSCLE RELAXATION

SEE MUSCLE FUNCTION, MUSCLE RELAXATION

MUSCLE STIMULANTS

R01DE-05397-01 Craniofacial bone formation and muscle
activity (Rhesus monkey)

MUSCLE STRETCH RECEPTORS

SEE MUSCLE FUNCTION, MUSCLE STRETCH (RECEPTORS)

MUSCLE STRETCH REFLEX

SEE MUSCLE FUNCTION, MUSCLE STRETCH REFLEX

MUSCLE TENSION

SEE MUSCLE FUNCTION, MUSCLE TENSION

MUSCLE TRANSPLANTATION

**** R01DE-04857-02** Temporalis flaps in the treatment of facial
paralysis (monkeys)

MUSCLES, EAR MUSCLES, TENSOR TYMPANI

P01DE-01697-19 0035 A research program in craniofacial
problems - Non-human primate model of cleft palate
(monkeys)

MUSCLES, FACIAL MUSCLES

- R01DE-03794-09** Surgical-orthodontics and bone healing
(monkeys)
- ** R01DE-04047-05** Extensibility characteristics of human cheek
- R01DE-04157-08** Functional mandibular movements (human)
- R01DE-04227-07** Adaptations to changes in masticatory
muscle length (monkeys)
- R01DE-04610-03** Physiological studies on mastication
(human)
- R01DE-04884-13** Neural processes in somatic movement
(monkeys)
- R01DE-04940-04** Muscular disorders in craniofacial
malformations (human)
- R01DE-05396-02** Craniofacial adaptations after maxillary
osteotomy (monkeys)
- R01DE-05679-01** Pathophysiology of MPD and other facial
pain syndromes (animals)

MUSCLES, MYOFIBRILS

- R01DE-04889-04** Dental significance of jaw muscle silent
periods (human)
- R01DE-05112-03** Muscle activity and control in mastication
(mammals, lizards)
- R01DE-05495-02** Myofibroblast contraction in periodontium
(rats)

MUSCLES, MYOGENESIS

P01DE-02848-11 0003 Biology of connective tissue, bones,
and teeth - Mandibular morphogenesis-Embryonic neonatal
and postnatal development (mice)

MUSCLES, STRIATED MUSCLE

R01DE-05558-01 Sensory alterations of craniofacial form
(Rhesus monkeys)

MUSCULAR DISORDERS

SEE ALSO NEUROMOTOR DISORDERS, NEUROMUSCULAR
(GENERAL)

**** R01DE-04940-04** Muscular disorders in craniofacial
malformations (human)

MUTAGEN TESTS

SEE GENETICS, MUTAGENS, MUTAGEN TESTS

MUTANTS

SEE GENETICS, MUTATION, MUTANTS*

MUTATION

SEE GENETICS, MUTATION

MUTATION, CHROMOSOME

SEE GENETICS, MUTATION, GENE MUTATION

MYELOBLASTOSIS VIRUS AVIAN

SEE VIRUSES, RETROVIRIDAE, LEUKOSIS-SARCOMA AVIAN,
LEUKOSIS VIRUSES AVIAN

MYELOMA

SEE NEOPLASMS OF BLOOD AND RE SYSTEM, BONE MARROW
NEOPLASMS, MULTIPLE MYELOMA

MYELOMA-SPLEEN CELL HYBRIDS

SEE CELL HYBRIDS, HYBRIDOMAS

MYOFASCIAL PAIN-DYSFUNCTION SYNDROME

SEE ORAL-PHARYNGEAL DISORDERS, MPD SYNDROME

MYOFIBRILS

SEE MUSCLES, MYOFIBRILS

MYOGENESIS

SEE MUSCLES, MYOGENESIS

MYOGRAPHY, ELECTROMYOGRAPHY

SEE MUSCLE FUNCTION, ELECTROMYOGRAPHY*

MYONEURAL JUNCTION

SEE NEUROMOTOR SYSTEM, NEUROMUSCULAR JUNCTION

MYOTACTIC RECEPTORS

SEE MUSCLE FUNCTION, MUSCLE STRETCH (RECEPTORS)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

MYOTACTIC REFLEX

SEE MUSCLE FUNCTION, MUSCLE STRETCH REFLEX

MYRINGOPLASTY

SEE EAR SURGERY, MYRINGOPLASTY

N

SEE NITROGEN

N ANTIGEN

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

NA

SEE SODIUM

NADP(H2)

SEE PYRIDINE NUCLEOTIDES, NICOTINAMIDE RIBOTIDES, NADP(H2)

NALOXONE

SEE ALKALOIDS, MORPHINES, NALOXONE

NAPHTHALENES, METHYLENEDIOXY-, PODOPHYLLIN

R23DE-05393-03 Factors association with hyperplasia of oral mucosa

NAPHTHYLAMINES, PROPRANOLOL

R23DE-05142-03 Control mechanisms in salivary gland development (rats)

NARCOTICS RECEPTORS

SEE NEUROTRANSMITTERS RECEPTORS, ENDORPHIN RECEPTORS

NASAL (INCLUDES NOSE, OLFACTION AND PARANASAL SINUSES)

R01DE-04731-05 Analysis of primary palate formation (chick embryo)

NASAL, NOSE

** P01DE-01697-19 0040 A research program in craniofacial problems - Pattern recognition for reconstruction of nasal capsular anatomy

** P01DE-02872-12 0053 Craniofacial dysmorphology - Maxillofacial prosthetics (human)

R01DE-05145-03 Adjustive cranial skeletal growth (rats)

R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)

R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)

P01DE-05837-01 0002 Growth, surgical, and speech aspects of cleft palate - Maxillofacial growth (dogs, tamarins)

NASAL, PARANASAL SINUSES

R01DE-04731-05 Analysis of primary palate formation (chick embryo)

R01DE-05659-01 Surgical and radiographic evaluation of the temporomandibular joint (human)

NASOPHARYNX

SEE ORAL-PHARYNGEAL, NASOPHARYNX

NATURAL KILLER CELLS

SEE BLOOD CELLS, LYMPHOCYTES, KILLER CELLS

NATURAL KILLER LYMPHOCYTES

SEE BLOOD CELLS, LYMPHOCYTES, KILLER CELLS

NATURAL PRODUCTS

SEE ALSO BIOLOGICAL PREPARATIONS AND STANDARDIZATION

N01DE-02427-04 Synthesize noncariogenic sweeteners

NECK

SEE BODY REGIONS, NECK

NECK NEOPLASMS

SEE NEOPLASMS OF BODY REGIONS, HEAD AND NECK

NECROCYTOSIS

SEE CELL DEATH

NEGROES

SEE SOCIAL GROUPS, ETHNIC, AMERICANS, BLACK AMERICANS

NEISSERIA

SEE BACTERIA, NEISSERIAEAE, NEISSERIA*

NEONATAL

SEE AGE (ANIMAL), INFANTS NEWBORN

SEE CHILDREN, INFANT NEWBORN (BIRTH TO 4-6 WKS)

NEOPLASMS, ADENOCARCINOMA

R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)

NEOPLASMS, CARCINOMA

SEE ALSO NEOPLASMS, ADENOCARCINOMA

R01DE-05525-02 Nature of the permeability barrier in oral epithelium

NEOPLASMS, CARCINOMA EPIDERMIOID

P50DE-02731-15 0032 Development support for dental research institute - Epithelial cell basal lamina biosynthesis (rats)

R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)

R23DE-05117-03 Enhancement of oral cancer after allografting (mice)

R01DE-05330-02 Herpes virus antibodies in patients with oral cancer

R23DE-05393-03 Factors association with hyperplasia of oral mucosa

NEOPLASMS, FIBROSARCOMA

R23DE-05117-03 Enhancement of oral cancer after allografting (mice)

NEOPLASMS, RADIATION INDUCED

SEE ALSO NEOPLASTIC TRANSFORMATION, CARCINOGENESIS, RADIATION

R01DE-03996-06 Low level irradiation-modification of carcinogenesis

NEOPLASMS CLASSIFICATION AND STAGING

R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

NEOPLASMS COMBINATION THERAPY

SEE NEOPLASTIC THERAPY, COMBINATION ANTINEOPLASTIC THERAPY

NEOPLASMS DIAGNOSIS, IMMUNODIAGNOSIS OF NEOPLASMS

R01DE-05330-02 Herpes virus antibodies in patients with oral cancer

NEOPLASMS IMMUNODIAGNOSIS

SEE NEOPLASMS DIAGNOSIS, IMMUNODIAGNOSIS OF NEOPLASMS

NEOPLASMS IMMUNOLOGY

SEE ALSO NEOPLASMS DIAGNOSIS, IMMUNODIAGNOSIS OF NEOPLASMS

R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)

R23DE-05117-03 Enhancement of oral cancer after allografting (mice)

R01DE-05330-02 Herpes virus antibodies in patients with oral cancer

NEOPLASMS METASTASIS

SEE NEOPLASTIC GROWTH, NEOPLASMS METASTASIS

NEOPLASMS OF BLOOD AND RE SYSTEM, BONE MARROW NEOPLASMS, MULTIPLE MYELOMA

R01DE-05467-02 Pathogenesis of localized bone destruction

NEOPLASMS OF BLOOD AND RE SYSTEM, LEUKEMIA

P50DE-02670-15 0035 Institute of Dental Research - Granulocyte growth and division

NEOPLASMS OF BLOOD AND RE SYSTEM, LYMPHOMA

R01DE-05467-02 Pathogenesis of localized bone destruction

NEOPLASMS OF BODY REGIONS, HEAD AND NECK

SEE ALSO NEOPLASMS OF ORAL-PHARYNGEAL STRUCTURES

R01DE-03666-07 X-ray therapeutic index for salivary glands

NEOPLASMS OF ORAL-PHARYNGEAL STRUCTURES

R01DE-05525-02 Nature of the permeability barrier in oral epithelium

NEOPLASMS OF ORAL-PHARYNGEAL STRUCTURES, LIP NEOPLASMS

** R23DE-05117-03 Enhancement of oral cancer after allografting (mice)

NEOPLASMS OF ORAL-PHARYNGEAL STRUCTURES, MOUTH NEOPLASMS

R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)

** R01DE-05330-02 Herpes virus antibodies in patients with oral cancer

NEOPLASMS OF ORAL-PHARYNGEAL STRUCTURES, SALIVARY GLAND NEOPLASMS

R01DE-03666-07 X-ray therapeutic index for salivary glands

NEOPLASMS OF REPRODUCTIVE SYSTEM FEMALE, UTERUS NEOPLASMS, CERVIX NEOPLASMS

R01DE-05330-02 Herpes virus antibodies in patients with oral cancer

NEOPLASMS OF SKELETAL SYSTEM, BONE NEOPLASMS

SEE ALSO NEOPLASMS OF SKELETAL SYSTEM, OSTEOGENIC SARCOMA

R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)

NEOPLASMS OF SKELETAL SYSTEM, OSTEOGENIC SARCOMA

R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)

NEOPLASMS OF SKIN

R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)

NEOPLASMS STAGING

SEE NEOPLASMS CLASSIFICATION AND STAGING

NEOPLASMS SURGERY

** R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

NEOPLASTIC CELLS, HELA CELLS

R01DE-04096-05 Biocompatibility of endodontic materials (animals)

NEOPLASTIC GROWTH

** R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

R23DE-05117-03 Enhancement of oral cancer after allografting (mice)

NEOPLASTIC GROWTH, NEOPLASMS METASTASIS

R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

NEOPLASTIC THERAPY, CANCER CHEMOTHERAPY

** P50DE-02600-15 0034 Support for oral biology research center - Salivary and oral mucosal changes after cancer chemotherapy

** R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

NEOPLASTIC THERAPY, CANCER RADIOTHERAPY

SEE ALSO RADIATION SENSITIVITY, RADIOSENSITIZERS

** R01DE-03666-07 X-ray therapeutic index for salivary glands

NEOPLASTIC THERAPY, COMBINATION ANTINEOPLASTIC THERAPY

R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

NEOPLASTIC TRANSFORMATION, CARCINOGENESIS (GENERAL)

R01DE-05838-02 Morphogenetic role of glycosaminoglycans (chick embryo)

NEOPLASTIC TRANSFORMATION, CARCINOGENESIS, CHEMICAL

** R01DE-03996-06 Low level irradiation-modification of carcinogenesis

NEOPLASTIC TRANSFORMATION, CARCINOGENESIS, RADIATION

** R01DE-03996-06 Low level irradiation-modification of carcinogenesis

NEOPLASTIC TRANSFORMATION, CARCINOGENESIS, VIRAL

P50DE-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus

P50DE-02658-15 0176 Regional dental research center - Collagen biochemistry and the myeloblastosis associated virus infected cells

R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine

R01DE-05330-02 Herpes virus antibodies in patients with oral cancer

** R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)

NEOPLASTIC TRANSFORMATION, CARCINOGENS, CHEMICAL

R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)

NEOPLASTIC TRANSFORMATION, CARCINOGENS, COCARCINOGENS

** R01DE-03996-06 Low level irradiation-modification of carcinogenesis

NEOSYNEPHRINE

SEE PHENOLIC AMINES, NEOSYNEPHRINE

NERVE CELLS

SEE NERVOUS SYSTEM, NEURONS

NERVE GROWTH FACTOR

SEE GROWTH FACTORS (INCL. ANABOLICS), NERVE GROWTH FACTOR

NERVE IMPULSE FACILITATION

SEE NEUROPHYSIOLOGY, NERVE IMPULSE FACILITATION

NERVE IMPULSE INHIBITION

SEE NEUROPHYSIOLOGY, NERVE IMPULSE INHIBITION

NERVE IMPULSE INITIATION

SEE NEUROPHYSIOLOGY, NERVE IMPULSE INITIATION

NERVE REGENERATION

SEE NERVOUS SYSTEM REGENERATION

NERVE TRANSMITTER SUBSTANCES

SEE NEUROTRANSMITTERS AND NEUROMODULATORS (GENERAL)

NERVOUS DISORDERS CENTRAL, ENCEPHALITIS

R23DE-05572-02 NEW antiviral therapy for oral and other herpes (mice, guinea pig, rabbits)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects. See Appendix for investigator's name and Grant Number.

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NERVOUS DISORDERS DIAGNOSIS (INCL EXAMS)*

SEE ALSO BRAIN ELECTRICAL ACTIVITY
SEE ALSO NEUROMOTOR DISORDERS DIAGNOSIS (INCL EXAMS)*

- P500E-02668-15 0204 Regional dental research center - Psychophysical measures of combined tactile and thermal sensitivity (human)

NERVOUS DISORDERS PERIPHERAL, FACIAL PARALYSIS

- ** R01DE-04857-02 Temporalis flaps in the treatment of facial paralysis (monkeys)

NERVOUS DISORDERS PERIPHERAL, TRIGEMINAL NEURALGIA

- R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)
** R01OE-05204-03 Operant neural control in trigeminal pain systems (rat)

NERVOUS SYSTEM, AFFERENT NERVES

- P500E-02668-15 0200 Regional dental research center - Response of first order mechanoreceptive afferents to moving tactile stimuli
P500E-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli
R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)
R01DE-04884-13 Neural processes in somatic movement (monkeys)
R01DE-04889-04 Dental significance of jaw muscle silent periods (human)
R01OE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)
R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

NERVOUS SYSTEM, AFFERENT NERVES, CUTANEOUS SENSORY NERVES

- R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)

NERVOUS SYSTEM, CRANIAL NERVES

- P500E-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)

NERVOUS SYSTEM, CRANIAL NERVES, ACOUSTIC NERVE

- P500E-02668-15 0214 Regional dental research center -

NERVOUS SYSTEM, CRANIAL NERVES, LARYNGEAL NERVES

- R01DE-05728-01 Role of chemoreceptors in craniofacial function (lambs)

NERVOUS SYSTEM, CRANIAL NERVES, TRIGEMINAL NERVE

SEE ALSO NERVOUS DISORDERS PERIPHERAL, TRIGEMINAL NEURALGIA

- P500E-02668-15 0196 Regional dental research center - Cytochemical demonstration of macromolecules of craniofacial tissue
P500E-02668-15 0197 Regional dental research center - Peripheral nerves of the orofacial region
R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)
R01DE-04884-13 Neural processes in somatic movement (monkeys)
R01DE-04889-04 Dental significance of jaw muscle silent periods (human)
** P01OE-05130-03 0009 Dental/orofacial pain--Mechanisms behavior and modulation - Dental near and far field potentials and pain reactivity (cats, monkeys)
R01OE-05159-03 Distribution and ultrastructure of dental innervation (cats, rats)
R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)
R01OE-05204-03 Operant neural control in trigeminal pain systems (rat)
R01DE-05208-03 Mechanism of dental and facial sensation (monkeys)
R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)
** R01DE-05574-01 Neural aspects of craniofacial morphogenesis (frogs)

NERVOUS SYSTEM, GANGLIA

- R23DE-05491-02 Control of biomineralization in two species (snails)
R23DE-05572-02 NEW antiviral therapy for oral and other herpes (mice, guinea pig, rabbits)

NERVOUS SYSTEM, NERVE ENDINGS, SYNAPSES

- R01OE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

NERVOUS SYSTEM, NERVES, INNERVATION (GENERAL)

- ** P500E-02668-15 0211 Regional dental research center - Salivary glands and their innervation in diabetes (mice)
R01DE-03794-09 Surgical-orthodontics and bone healing (monkeys)

- R01DE-05078-05 Craniofacial growth and remodeling (human)

- ** R01DE-05159-03 Distribution and ultrastructure of dental innervation (cats, rats)
R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)
R01DE-05832-01 Organization of the trigeminal mesencephalic nucleus (monkeys, opossums)

NERVOUS SYSTEM, NEUROEFFECTORS

SEE ALSO NEUROMOTOR SYSTEM, NEUROMUSCULAR JUNCTION

- ** R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

NERVOUS SYSTEM, NEURONS

SEE ALSO NEUROMOTOR SYSTEM, MOTOR NEURONS

- ** P500E-02668-15 0199 Regional dental research center - Mechanisms governing the behavior of somatosensory cerebral cortical neurons
** P500E-02668-15 0200 Regional dental research center - Response of first order mechanoreceptive afferents to moving tactile stimuli
P500E-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli
** P500E-02668-15 0209 Regional dental research center - Static and dynamic properties of S-I neurons in the behaving macaque monkey
R01OE-05194-03 Latency of herpes simplex in oro-facial infections (human)

NERVOUS SYSTEM, NEURONS, AXONS

- R01OE-05159-03 Distribution and ultrastructure of dental innervation (cats, rats)

NERVOUS SYSTEM, NEURONS, INTERNEURONS

- R01DE-04884-13 Neural processes in somatic movement (monkeys)

NERVOUS SYSTEM, PERIPHERAL NERVES (GENERAL)

- ** P500E-02668-15 0197 Regional dental research center - Peripheral nerves of the orofacial region
** R01OE-05832-01 Organization of the trigeminal mesencephalic nucleus (monkeys, opossums)

NERVOUS SYSTEM, SPINAL NERVES

- R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)

NERVOUS SYSTEM AUTONOMIC

- R01DE-02110-17 Salivary gland structure and function (rats)
P500E-02668-15 0197 Regional dental research center - Peripheral nerves of the orofacial region
R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)
R01DE-04897-02 Functional development of salivary glands (rats)
R01DE-05159-03 Distribution and ultrastructure of dental innervation (cats, rats)
R23DE-05605-01 The humoral regulation of pulp circulation (rats)

NERVOUS SYSTEM AUTONOMIC, PARASYMPATHETIC NERVOUS SYSTEM

SEE ALSO NERVOUS SYSTEM, CRANIAL NERVES, LARYNGEAL NERVES

SEE ALSO NEUROTRANSMITTERS RECEPTORS, CHOLINERGIC RECEPTORS

- P500E-02668-15 0197 Regional dental research center - Peripheral nerves of the orofacial region
R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)
R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

NERVOUS SYSTEM AUTONOMIC, SYMPATHETIC NERVOUS SYSTEM

SEE ALSO NEUROTRANSMITTERS RECEPTORS, ADRENERGIC RECEPTORS

- P500E-02668-15 0197 Regional dental research center - Peripheral nerves of the orofacial region
R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)
R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

NERVOUS SYSTEM CENTRAL

- P500E-02668-15 0199 Regional dental research center - Mechanisms governing the behavior of somatosensory cerebral cortical neurons
P500E-02668-15 0200 Regional dental research center - Response of first order mechanoreceptive afferents to moving tactile stimuli
R01OE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)
** R01DE-05832-01 Organization of the trigeminal mesencephalic nucleus (monkeys, opossums)

NERVOUS SYSTEM CENTRAL, NEURAL CANAL

- ** R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

NERVOUS SYSTEM REGENERATION

- R23DE-05491-02 Control of biomineralization in two species (snails)

NEURAL CANAL

SEE NERVOUS SYSTEM CENTRAL, NEURAL CANAL

NEURAL CONDUCTION

SEE NEUROPHYSIOLOGY, NEURAL CONDUCTION

NEURAL CONTROL (MECHANISMS)

SEE INFORMATION PROCESSING AND CONTROL (NEURAL)

NEURAL ENCODING (MECHANISMS)

SEE INFORMATION PROCESSING AND CONTROL (NEURAL)

NEURAL PROCESSING AND CONTROL

SEE INFORMATION PROCESSING AND CONTROL (NEURAL)

NEURAL TRANSMISSION

SEE NEUROPHYSIOLOGY, NEURAL TRANSMISSION

NEURAL TRANSMITTERS, BIOGENIC AMINES

SEE NEUROTRANSMITTERS AND NEUROMODULATORS (GENERAL)

NEURAL TUBE AND PLATE DEFECTS

SEE CONGENITAL ABNORMALITIES, FUSION FAILURES

NEUROCHEMISTRY

SEE ALSO NEUROTRANSMITTERS BIOSYNTHESIS
R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

NEUROEFFECTORS

SEE NERVOUS SYSTEM, NEUROEFFECTORS

NEUROGENESIS

SEE NEUROLOGY, DEVELOPMENTAL, NEUROGENESIS

NEUROHORMONES

SEE ALSO GROWTH FACTORS (INCL. ANABOLICS), NERVE GROWTH FACTOR

SEE ALSO NEUROTRANSMITTERS AND NEUROMODULATORS (GENERAL)

SEE ALSO NEUROTRANSMITTERS BIOSYNTHESIS

- R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

NEUROHUMORS (GENERAL)

SEE NEUROTRANSMITTERS AND NEUROMODULATORS (GENERAL)

NEUROHUMORS BIOSYNTHESIS

SEE NEUROTRANSMITTERS BIOSYNTHESIS

NEUROLOGIC EXAMINATIONS

SEE NERVOUS DISORDERS DIAGNOSIS (INCL EXAMS)*

NEUROLOGIC MANIFESTATIONS

P500E-02668-15 0199 Regional dental research center - Mechanisms governing the behavior of somatosensory cerebral cortical neurons

P500E-02668-15 0200 Regional dental research center - Response of first order mechanoreceptive afferents to moving tactile stimuli

NEUROLOGICAL SCIENCES STUDY SECTION

- ** R01OE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

NEUROLOGY, DEVELOPMENTAL

SEE ALSO CHILO MENTAL DEVELOPMENT

- ** R01OE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)

NEUROLOGY, DEVELOPMENTAL, NEUROGENESIS

SEE ALSO NERVOUS SYSTEM REGENERATION

- ** R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

- ** R01OE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)

NEUROLOGY A STUDY SECTION

- ** R01OE-05208-03 Mechanism of dental and facial sensation (monkeys)

NEUROLOGY B STUDY SECTION

- ** R01DE-04884-13 Neural processes in somatic movement (monkeys)

NEUROMODULATORS

SEE NEUROTRANSMITTERS AND NEUROMODULATORS (GENERAL)

NEUROMOTOR DISORDERS, NEUROMUSCULAR (GENERAL)

- ** R01DE-04889-04 Dental significance of jaw muscle silent periods (human)
R01DE-04940-04 Muscular disorders in craniofacial malformations (human)

NEUROMOTOR DISORDERS DIAGNOSIS (INCL EXAMS)*

P500E-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)

NEUROMOTOR EXAMINATIONS

SEE NEUROMOTOR DISORDERS DIAGNOSIS (INCL EXAMS)*

NEUROMOTOR SYSTEM, MOTOR NEURONS

- ** R01DE-04884-13 Neural processes in somatic movement (monkeys)
P500E-04898-05 0004 Periodontal disease research center - Periodontal disease and the electromyographic silent period (human)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

(contd.)

NEUROMOTOR SYSTEM, NEUROMUSCULAR ASPECTS (GENERAL)

- ** P50DE-02668-15 0214 Regional dental research center -
- ** R01DE-03610-15 0018 Cranio-facial growth and development - Function and growth of the temporomandibular joint (monkeys)
- R01DE-05397-01 Craniofacial bone formation and muscle activity (Rhesus monkey)
- R01DE-05558-01 Sensory alterations of craniofacial form (Rhesus monkeys)

NEUROMOTOR SYSTEM, NEUROMUSCULAR JUNCTION

- R01DE-04164-06 Functional properties of mammalian masticatory muscles

NEUROMOTOR SYSTEM, NEUROMUSCULAR TRANSMISSION

- SEE ALSO MUSCLE FUNCTION, MUSCLE CONTRACTION
- R01DE-04884-13 Neural processes in somatic movement (monkeys)
- R01DE-04889-04 Dental significance of jaw muscle silent periods (human)

NEUROMOTOR SYSTEM, SENSORIMOTOR SYSTEMS (GENERAL)

- P50DE-02668-15 0199 Regional dental research center - Mechanisms governing the behavior of somatosensory cerebral cortical neurons
- P50DE-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli
- ** R01DE-05558-01 Sensory alterations of craniofacial form (Rhesus monkeys)

NEUROMUSCULAR ASPECTS

- SEE NEUROMOTOR SYSTEM, NEUROMUSCULAR ASPECTS (GENERAL)

NEUROMUSCULAR DISORDERS

- SEE NEUROMOTOR DISORDERS, NEUROMUSCULAR (GENERAL)

NEUROMUSCULAR JUNCTION

- SEE NEUROMOTOR SYSTEM, NEUROMUSCULAR JUNCTION

NEUROMUSCULAR STIMULANTS

- SEE MUSCLE STIMULANTS

NEUROMUSCULAR SYSTEM

- SEE NEUROMOTOR SYSTEM, NEUROMUSCULAR ASPECTS (GENERAL)

NEUROMUSCULAR TRANSMISSION

- SEE NEUROMOTOR SYSTEM, NEUROMUSCULAR TRANSMISSION

NEURONS

- SEE NERVOUS SYSTEM, NEURONS

NEUROPHARMACOLOGICAL AGENTS, ANALGESICS

- R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis (cats)

NEUROPHARMACOLOGICAL AGENTS, ANTICONVULSANTS

- P50DE-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)
- R01DE-05459-02 Phenytoin--Pathogenesis of gingival overgrowth (cats)

NEUROPHARMACOLOGICAL AGENTS, PARASYMPATHOLYTIC

- R01DE-01554-20 Host factors in caries resistance (human, rats)

NEUROPHARMACOLOGICAL AGENTS, PARASYMPATHOMIMETIC

- SEE ALSO CHOLINE, ACETYLCHOLINE
- SEE ALSO IMIDAZOLES, HISTAMINE
- SEE ALSO MUSCLE STIMULANTS
- SEE ALSO NEUROTRANSMITTERS RECEPTORS, CHOLINERGIC RECEPTORS
- R01DE-05249-02 Salivary secretion-role of calcium (mice)

NEUROPHARMACOLOGICAL AGENTS, SYMPATHOLYTIC

- SEE ALSO CARDIOVASCULAR AGENTS, VASODILATORS
- R01DE-01554-20 Host factors in caries resistance (human, rats)
- R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)

NEUROPHARMACOLOGICAL AGENTS, SYMPATHOMIMETIC

- SEE ALSO BENZOPYRROLES, SEROTONIN
- SEE ALSO NEUROTRANSMITTERS RECEPTORS, ADRENERGIC RECEPTORS
- SEE ALSO PHENYLALKYLAMINES, CATECHOLAMINES
- SEE ALSO PHENYLALKYLAMINES, CATECHOLAMINES, EPINEPHRINE
- SEE ALSO PHENYLALKYLAMINES, CATECHOLAMINES, NOREPINEPHRINE
- R01DE-05249-02 Salivary secretion-role of calcium (mice)

NEUROPHARMACOLOGY

- R01DE-04004-07 Acupuncture and perception of dental pain (human)

- R01DE-05208-03 Mechanism of dental and facial sensation (monkeys)
- R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

NEUROPHYSIOLOGY (GENERAL)

- SEE ALSO BRAIN ELECTRICAL ACTIVITY
- SEE ALSO ELECTROPHYSIOLOGY
- SEE ALSO INFORMATION PROCESSING AND CONTROL (NEURAL)
- ** P50DE-02668-15 0210 Regional dental research center - Somesthetic capacities of human subjects (monkeys)
- ** R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)
- R01DE-04884-13 Neural processes in somatic movement (monkeys)
- R01DE-04889-04 Dental significance of jaw muscle silent periods (human)
- R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)

NEUROPHYSIOLOGY, NERVE IMPULSE FACILITATION

- P50DE-02668-15 0209 Regional dental research center - Static and dynamic properties of S-I neurons in the behaving macaque monkey

NEUROPHYSIOLOGY, NERVE IMPULSE INHIBITION

- P50DE-02668-15 0209 Regional dental research center - Static and dynamic properties of S-I neurons in the behaving macaque monkey

NEUROPHYSIOLOGY, NERVE IMPULSE INITIATION

- P50DE-02668-15 0209 Regional dental research center - Static and dynamic properties of S-I neurons in the behaving macaque monkey

NEUROPHYSIOLOGY, NEURAL CONDUCTION

- ** R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

NEUROPHYSIOLOGY, NEURAL TRANSMISSION

- SEE ALSO ELECTROPOTENTIALS, ACTION POTENTIALS
- SEE ALSO ELECTROPOTENTIALS, EVOKED POTENTIALS
- SEE ALSO EYE, VISUAL FEEDBACK
- SEE ALSO NEUROMOTOR SYSTEM, NEUROMUSCULAR TRANSMISSION

- R01DE-05208-03 Mechanism of dental and facial sensation (monkeys)
- R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)
- R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)

NEUROPHYSIOLOGY, NEURAL TRANSMISSION, ANTIDROMIC IMPULSES

- R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)

NEUROPHYSIOLOGY, REFLEX, SOMATIC REFLEXES

- ** P50DE-02668-15 0209 Regional dental research center - Static and dynamic properties of S-I neurons in the behaving macaque monkey

NEUROREGULATORS

- SEE NEUROTRANSMITTERS AND NEUROMODULATORS (GENERAL)

NEUROSIS

- SEE PSYCHOLOGY ABNORMAL, NEUROSIS

NEUROSURGERY

- R01DE-05208-03 Mechanism of dental and facial sensation (monkeys)

NEUROTRANSMITTERS AND

NEUROMODULATORS (GENERAL)

- SEE ALSO AMINO ACIDS, GAMMA-AMINOBUTYRIC ACID
- SEE ALSO BENZOPYRROLES, SEROTONIN
- SEE ALSO CHOLINE, ACETYLCHOLINE
- SEE ALSO DICARBOXYLIC AMINO ACIDS, ASPARTIC ACID
- SEE ALSO DICARBOXYLIC AMINO ACIDS, GLUTAMATES
- SEE ALSO IMIDAZOLES, HISTAMINE
- SEE ALSO PEPTIDES, ENKEPHALIN
- SEE ALSO PHENYLALKYLAMINES, CATECHOLAMINES, EPINEPHRINE
- SEE ALSO PHENYLALKYLAMINES, CATECHOLAMINES, NOREPINEPHRINE
- R01DE-03469-10 Teratogens effects on cleft palate formation (mice)
- R01DE-04897-02 Functional development of salivary glands (rats)
- ** R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)
- R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis (cats)
- R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)

NEUROTRANSMITTERS BIOSYNTHESIS

- R01DE-03469-10 Teratogens effects on cleft palate formation (mice)
- R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

NEUROTRANSMITTERS RECEPTORS

- R01DE-03469-10 Teratogens effects on cleft palate formation (mice)
- R01DE-04889-04 Dental significance of jaw muscle silent periods (human)

NEUROTRANSMITTERS RECEPTORS, ADRENERGIC RECEPTORS

- R01DE-02110-17 Salivary gland structure and function (rats)
- R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

NEUROTRANSMITTERS RECEPTORS, ADRENERGIC RECEPTORS, ALPHA RECEPTORS

- R01DE-04897-02 Functional development of salivary glands (rats)
- R01DE-05632-01 Development of salivary gland secretory function (rats)
- R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)
- R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

NEUROTRANSMITTERS RECEPTORS, ADRENERGIC RECEPTORS, BETA RECEPTORS

- R01DE-04897-02 Functional development of salivary glands (rats)
- R23DE-05142-03 Control mechanisms in salivary gland development (rats)
- ** R01DE-05550-01 Cell death during craniofacial embryogenesis
- R01DE-05632-01 Development of salivary gland secretory function (rats)
- R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)
- R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

NEUROTRANSMITTERS RECEPTORS, ADRENERGIC RECEPTORS, DOPAMINERGIC RECEPTORS

- R01DE-02110-17 Salivary gland structure and function (rats)

NEUROTRANSMITTERS RECEPTORS, CHOLINERGIC RECEPTORS

- R01DE-04897-02 Functional development of salivary glands (rats)
- R01DE-05632-01 Development of salivary gland secretory function (rats)
- R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)
- R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

NEUROTRANSMITTERS RECEPTORS, ENDOPHIN RECEPTORS

- ** R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)

NEUTROPHIL LEUKOCYTES

- SEE BLOOD CELLS, LEUKOCYTES, NEUTROPHILS

NEWBORN

- SEE CHILDREN, INFANT NEWBORN (BIRTH TO 4-6 WKS)

NI

- SEE METALS, HEAVY METALS, NICKEL (COMPOUNDS)

NICKEL (COMPOUNDS)

- SEE METALS, HEAVY METALS, NICKEL (COMPOUNDS)

NICOTINAMIDE ADENINE DINUCLEOTIDE PHOSPHATE (REDUCED)

- SEE PYRIDINE NUCLEOTIDES, NICOTINAMIDE RIBOTIDES, NADP (H2)

NICOTINIC RECEPTORS

- SEE NEUROTRANSMITTERS RECEPTORS, CHOLINERGIC RECEPTORS

NITROGEN

- ** R01DE-04335-05 Comparison of treatment procedures used in endodontics

NITROUS OXIDE

- R01DE-04004-07 Acupuncture and perception of dental pain (human)
- ** R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

NK-CELLS

- SEE BLOOD CELLS, LYMPHOCYTES, KILLER CELLS

NOCARDIA DENTOCARIOSUS

- SEE BACTERIA, ACTINOMYCETALES, ROTHIA DENTOCARIOSUS

NONCHROMOSOMAL DNA, GENETICS, INHERITANCE

- SEE GENETICS, EXTRACHROMOSOMAL INHERITANCE

NON-INVASIVE DIAGNOSIS (DIAGNOSTIC TECHNIQUES)

- SEE DIAGNOSTIC TESTS, NON-INVASIVE*

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects. See Appendix for investigator's name and Grant Number.

(contd.)

NON**NON-NUTRITIONAL DISORDERS, NUTRITION THERAPY FOR**

SEE NUTRITION, NUTRITION THERAPY (NON-NUTRITIONAL DISORDERS)

NORADRENALINE

SEE PHENYLALKYLAMINES, CATECHOLAMINES, NOREPINEPHRINE

NOREPINEPHRINE

SEE PHENYLALKYLAMINES, CATECHOLAMINES, NOREPINEPHRINE

NOSE

SEE NASAL, NOSE

NUCLEASES, DEOXYRIBONUCLEASE

P500E-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology
R01DE-05684-01 Saliva proteins—Chemistry, genetics and oral health

NUCLEASES, RIBONUCLEASE

P500E-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology
R01DE-05684-01 Saliva proteins—Chemistry, genetics and oral health

NUCLEIC ACIDS, DNA

SEE ALSO GENETICS, EXTRACHROMOSOMAL INHERITANCE
SEE ALSO NUCLEIC ACIDS SYNTHESIS, DNA
P500E-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
P500E-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus
P500E-02623-14 0014 Center for oral health research - Surface receptors on plaque forming organisms
** P500E-02731-15 0019 Development support for dental research institute - Structure and maintenance of extrachromosomal DNA in streptococci
R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)
R01DE-04224-07 Genetics of oral microflora
R01DE-04511-06 Stability of differentiation—Craniofacial study (human, hamsters)
R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
R01DE-05395-02 Stem cells in oral mucosa
R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)
R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
R01DE-06000-01 Effect of parotid function on saliva and cells

NUCLEIC ACIDS, DNA BACTERIAL

R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
** R01DE-05218-03 DNA homologies among bacteria of periodontal diseases

NUCLEIC ACIDS, RNA

SEE ALSO NUCLEIC ACIDS SYNTHESIS, RNA
P500E-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
P500E-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus
R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)
R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
R01DE-06000-01 Effect of parotid function on saliva and cells

NUCLEIC ACIDS, MRNA

SEE ALSO GENETICS, GENETIC CODING
P500E-02600-15 0023 Support for oral biology research center - Regulation of antibody response (mice, rabbits)
P500E-02670-15 0033 Institute of Dental Research - Genetic and biochemical basis for S mutants virulence (rats)
P01DE-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)
R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)

NUCLEIC ACIDS CLONING

R01DE-04224-07 Genetics of oral microflora

NUCLEIC ACIDS INHIBITORS

R01DE-05089-03 Oral herpes simplex—An approach to dental therapy (hamsters)

NUCLEIC ACIDS METABOLISM

SEE ALSO NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)*
R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)

NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)

R01DE-04511-06 Stability of differentiation—Craniofacial study (human, hamsters)

NUCLEIC ACIDS STRUCTURE, NUCLEOSIDES (TIDES) SEQUENCE

R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine

NUCLEIC ACIDS SYNTHESIS, DNA

SEE ALSO NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)
R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)
R01DE-04731-05 Analysis of primary palate formation (chick embryo)
R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
P500E-05139-04 0002 Clinical research center for periodontal disease - Immunological investigations
R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)
R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
R01DE-05999-01 The role of nutrition in oral health

NUCLEIC ACIDS SYNTHESIS, RNA

SEE ALSO GENETICS, GENETIC REGULATION, GENETIC INDUCTION-REPRESSION-DEPRESSION, TRANSCRIPTION
R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)

NUCLEOSIDE MONOPHOSPHATES CYCLIC

SEE NUCLEOTIDES, NUCLEOSIDE MONOPHOSPHATES CYCLIC

NUCLEOSIDES, ARABINONUCLEOSIDES

SEE ALSO PURINE NUCLEOSIDES, ADENINE NUCLEOSIDES, ADENINE ARABINOSIDE
** R01DE-05089-03 Oral herpes simplex—An approach to dental therapy (hamsters)

NUCLEOSIDES ANALOGS

** R01DE-05089-03 Oral herpes simplex—An approach to dental therapy (hamsters)

NUCLEOSIDES (TIDES) SEQUENCE

SEE NUCLEIC ACIDS STRUCTURE, NUCLEOSIDES (TIDES) SEQUENCE

NUCLEOTIDES

SEE ALSO PURINE NUCLEOTIDES
SEE ALSO PYRIDINE NUCLEOTIDES
SEE ALSO PYRIMIDINE NUCLEOTIDES
R01DE-05483-02 Characterization of predental extracellular fluid (rats)

NUCLEOTIDES, NUCLEOSIDE

MONOPHOSPHATES CYCLIC
SEE ALSO PURINE NUCLEOTIDES, ADENINE NUCLEOTIDES, AMP CYCLIC

SEE ALSO PURINE NUCLEOTIDES, GUANINE NUCLEOTIDES, GMP CYCLIC

R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)
R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)
P500E-05139-04 0003 Clinical research center for periodontal disease
R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)
R01DE-05412-02 Electric current, bone remodeling and tooth movement (cats)
R01DE-05494-02 Activation of macrophages in periodontal disease
R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

NUCLEOTIDES, RIBONUCLEOTIDES

P500E-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus

NUCLEOTIDYL-CYCLASES, ADENYLATE

CYCLASE
P500E-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology
R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)
R01DE-03715-06 Cellular assembly—Its role in facial morphogenesis (lung)
R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)
** R01DE-05550-01 Cell death during craniofacial embryogenesis

NUCLEOTIDYL-CYCLASES, GUANYLATE

CYCLASE
R01DE-05466-03 Biochemical studies of a sweetener, SRI Oxime V (rats, mice, dogs, monkeys)

NUCLEUS-CYTOPLASM VOLUME**RELATIONSHIPS**

SEE CELL VOLUME

NULL(NUL) LYMPHOCYTES

SEE BLDD CELLS, LYMPHOCYTES, KILLER CELLS

NUTRIENT INTAKE ACTIVITY, BREAST FEEDING

R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)
R23DE-05006-03 Maternal malnutrition—Pregnancy immunology (human)

NUTRIENTS AND PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION

R23DE-05628-02 Influence of trace metals on dental health (rat)
N01DE-12434-0D Identify cariogenic elements of food

NUTRITION (GENERAL)

SEE ALSO FDDO
SEE ALSO GROWTH MEDIA
** P500E-02670-15 0020 Institute of Dental Research - Nutrition—Disease proneness during dental development

NUTRITION, DEVELOPMENTAL NUTRITION

SEE ALSO NUTRITION, MATERNAL-FETAL NUTRITION
** R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
R23DE-05006-03 Maternal malnutrition—Pregnancy immunology (human)
** R23DE-05628-02 Influence of trace metals on dental health (rat)

NUTRITION, DIET

P500E-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions
R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

NUTRITION, DIET, FASTING

SEE ALSO DRUGS, PHARMACOLOGY, BIOAVAILABILITY
SEE ALSO NUTRITIONAL ABNORMALITIES, STARVATION
P500E-02668-15 0192 Regional dental research center - Skeletal actions of calcitonin in the rat

NUTRITION, DIET PATHOGENIC

R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
R23DE-05628-02 Influence of trace metals on dental health (rat)

NUTRITION, DIET SCHEDULE AND ROUTE, TUBE FEEDING

** N01DE-92422-04 Dental plaque and saliva from gastric intubated patients

NUTRITION, DIET THERAPEUTIC,

HYPERALIMENTATION (THERAPY)
SEE ALSO NUTRITION, DIET SCHEDULE AND ROUTE, TUBE FEEDING

R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

NUTRITION, DIET THERAPEUTIC, VITAMIN THERAPY (ALL ROUTES OF ADMINISTRATION)

R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

NUTRITION, DIETARY CONSTITUENTS**(GENERAL)**

SEE ALSO GASTROINTESTINAL FUNCTION, ABSORPTION-TRANSPORT, DIETARY NUTRIENTS
P01DE-01850-18 0085 Nutritional sources and metabolic roles of fluoride - Absorption of fluoride from dietary substances (rats)
P01DE-01850-18 0086 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on serum alkaline phosphatase activity (mice)
P01DE-02847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism
R01DE-04795-05 Characteristics of cariogenic dental plaque
R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
R01DE-06000-01 Effect of parotid function on saliva and cells
N01DE-12434-0D Identify cariogenic elements of food

NUTRITION, DIETARY CONSTITUENTS,**CALORIC CONTENT**

SEE ALSO FDDO, SWEETENING AGENTS
R01DE-05999-01 The role of nutrition in oral health

NUTRITION, DIETARY CONSTITUENTS, DIETARY**CALCIUM**

R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
N01DE-12434-0D Identify cariogenic elements of food

NUTRITION, DIETARY CONSTITUENTS, DIETARY**CARBOHYDRATES**

P500E-02670-15 0020 Institute of Dental Research - Nutrition—Disease proneness during dental development
R01DE-03118-11 Inhibition of saccharide metabolism by oral flora
R01DE-04795-05 Characteristics of cariogenic dental plaque
R01DE-05531-03 Salivary immune factors (human, bacteria)
N01DE-12434-0D Identify cariogenic elements of food

NUTRITION, DIETARY CONSTITUENTS, DIETARY**IRON**

N01DE-12434-0D Identify cariogenic elements of food

NUTRITION, DIETARY CONSTITUENTS, DIETARY**LIPIDS**

N01DE-12434-0D Identify cariogenic elements of food (cont'd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

NUTRITION, DIETARY CONSTITUENTS, DIETARY PROTEINS

- ** R01DE-04278-06 Human saliva-streptococcal metabolic interactions
- R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)
- R01DE-05999-01 The role of nutrition in oral health
- N01DE-12434-00 Identify cariogenic elements of food

NUTRITION, DIETARY CONSTITUENTS, DIETARY SALTS

- N01DE-12434-00 Identify cariogenic elements of food

NUTRITION, DIETARY CONSTITUENTS, DIETARY TRACE ELEMENTS AND MINERALS

- SEE ALSO METALS, HEAVY METALS, CADMIUM (COMPOUNDS)
- SEE ALSO METALS, HEAVY METALS, CHROMIUM (COMPOUNDS)
- SEE ALSO METALS, HEAVY METALS, COBALT (COMPOUNDS)
- SEE ALSO METALS, HEAVY METALS, COPPER (COMPOUNDS)
- SEE ALSO METALS, HEAVY METALS, MANGANESE (COMPOUNDS)
- SEE ALSO METALS, HEAVY METALS, MOLYBDENUM (COMPOUNDS)
- SEE ALSO METALS, HEAVY METALS, ZINC (COMPOUNDS)
- SEE ALSO METALS, METALLOIDS, SELENIUM (COMPOUNDS)
- R01DE-01830-19 Quantitation of enamel demineralization mechanisms

- P01DE-01850-18 0068 Nutritional sources and metabolic roles of fluoride - Radioimmunoassay of parathyroid hormone in the rat
- ** P01DE-01850-18 0071 Nutritional sources and metabolic roles of fluoride - Fluoride content of infant, toddler and adult foods
- P50DE-02670-15 0020 Institute of Dental Research - Nutrition--Disease proneness during dental development
- R01DE-03856-07 Fluoride-selenium interaction in dental caries (rats)
- R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)
- R01DE-04615-04 Fluoride-cadmium interaction in dental caries (rats, human)
- R23DE-05037-03 Biochemical role of zinc in teeth and bones
- ** R23DE-05628-02 Influence of trace metals on dental health (rat)
- ** R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
- ** R01DE-05999-01 The role of nutrition in oral health

NUTRITION, DIETETICS

- SEE ALSO NUTRITIONAL REQUIREMENTS
- N01DE-12434-00 Identify cariogenic elements of food

NUTRITION, MATERNAL-FETAL NUTRITION

- ** R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)
- ** R23DE-05628-02 Influence of trace metals on dental health (rat)

NUTRITION, NUTRITION THERAPY (NON-NUTRITIONAL DISORDERS)

- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)

NUTRITION STUDY SECTION

- ** R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
- ** R23DE-05628-02 Influence of trace metals on dental health (rat)
- ** R01DE-05999-01 The role of nutrition in oral health

NUTRITION THERAPY (NON-NUTRITIONAL DISORDERS EXCEPT CANCER AND PRENEOPLASTIC CONDITIONS)

- SEE NUTRITION, NUTRITION THERAPY (NON-NUTRITIONAL DISORDERS)

NUTRITIONAL ABNORMALITIES, HYPERVITAMINOSIS

- ** P50DE-02668-15 0088 Regional dental research center - Hypervitaminosis D in lactation

NUTRITIONAL ABNORMALITIES, HYPOVITAMINOSIS A

- ** R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)

NUTRITIONAL ABNORMALITIES, HYPOVITAMINOSIS D

- SEE ALSO METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN
- R01DE-05413-02 Bone resorption in periodontal disease
- R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
- R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

NUTRITIONAL ABNORMALITIES, MALNUTRITION (GENERAL)

- P50DE-02670-15 0020 Institute of Dental Research - Nutrition--Disease proneness during dental development
- ** R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)
- ** R01DE-05999-01 The role of nutrition in oral health

NUTRITIONAL ABNORMALITIES, PROTEIN DEFICIENCY

- ** R01DE-05999-01 The role of nutrition in oral health

NUTRITIONAL ABNORMALITIES, STARVATION

- SEE ALSO NUTRITION, DIET, FASTING
- R23DE-05985-01 Growth factors in salivary secretions

NUTRITIONAL REQUIREMENTS

- P01DE-01850-18 0081 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on strain N mice
- R01DE-05144-03 Periodontal disease--Role of spirochetes (rabbits, human)

NUTRITIONAL REQUIREMENTS, DIETARY SUPPLEMENTS

- N01DE-12434-00 Identify cariogenic elements of food

NUTRITIONAL THERAPY (NON-NUTRITIONAL DISORDERS EXCEPT CANCER AND PRENEOPLASTIC CONDITIONS)

- SEE NUTRITION, NUTRITION THERAPY (NON-NUTRITIONAL DISORDERS)

NYSTATIN

- SEE ANTIBIOTICS, NYSTATIN

O

- SEE RESPIRATORY GASES, OXYGEN

OCCUPATIONAL DISEASES

- SEE OCCUPATIONAL HEALTH, OCCUPATIONAL DISEASES

OCCUPATIONAL HAZARDS

- SEE OCCUPATIONAL HEALTH, OCCUPATIONAL HAZARDS

OCCUPATIONAL HEALTH, OCCUPATIONAL DISEASES

- SEE ALSO METALS POISONING
- SEE ALSO OCCUPATIONAL HEALTH, OCCUPATIONAL HAZARDS
- R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

OCCUPATIONAL HEALTH, OCCUPATIONAL HAZARDS

- R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

OCCUPATIONS, JOB PERFORMANCE

- ** R23DE-05497-02 Dental disease and work loss (human)

OCTANOIC ACID

- SEE FATTY ACIDS, CAPRYLIC ACID

ODONTOBLASTS

- SEE DENTAL STRUCTURE, ODONTOBLASTS

OFFSPRING-MOTHER INTERACTION

- SEE FAMILY, PARENT-OFFSPRING, MOTHER-CHILD INTERACTION

OLD AGE

- SEE AGE (HUMAN), ADULT, OLD AGE (65 TO 99 YRS)

OLIGOSACCHARIDES

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
- R01DE-03118-11 Inhibition of saccharide metabolism by oral flora
- R01DE-04296-07 Lysozyme--Cell surface interactions and oral defense
- R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

ONCORNAVIRUSES

- SEE VIRUSES, RETROVIRIDAE

ONTOGENY

- SEE EMBRYOLOGY
- SEE GROWTH AND DEVELOPMENT
- SEE PREGNANCY, EMBRYO-FETUS

OPERANT CONDITIONING

- SEE PSYCHOLOGY, CONDITIONING, OPERANT

OPHTHALMOLOGY

- SEE EYE

OPIATE-LIKE PEPTIDES

- SEE PEPTIDES, ENKEPHALIN
- SEE PITUITARY-DIENCEPHALON HORMONES, ENDORPHINS

OPIATE RECEPTORS

- SEE NEUROTRANSMITTERS RECEPTORS, ENDORPHIN RECEPTORS

OPIATES

- SEE ALKALOIDS, OPIUM AND OPIATES

OPIUM

- SEE ALKALOIDS, OPIUM AND OPIATES

OPSONINS

- SEE IMMUNOLOGY, ANTIBODIES, OPSONINS

OPTICAL DATA STORAGE

- SEE COMPUTER, OPTICAL DATA STORAGE

OPTICAL MEMORIES (COMPUTER)

- SEE COMPUTER, OPTICAL DATA STORAGE

OPTICAL POLARIZATION*

- ** P50DE-02731-15 0037 Development support for dental research institute - Luminescence and polarized light in the diagnosis and treatment of caries

OPTICS, IMAGE PROCESSING ANALYSIS AND DISPLAY*

- ** P01DE-02872-12 0034 Craniofacial dysmorphology - Digitization of roentgencephalometric data (human)
- R01DE-03703-05 Integrated three-dimensional craniofacial measurement (human)
- R01DE-04610-03 Physiological studies on mastication (human)

OPTICS, LIGHT EMISSION, LUMINESCENCE*

- ** P50DE-02731-15 0037 Development support for dental research institute - Luminescence and polarized light in the diagnosis and treatment of caries

OPTICS, LIGHT SCATTERING*

- R01DE-05423-02 Diffuse reflectance by esthetic dental materials

OPTICS, MICROSCOPY, ELECTRON*

- R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)

OPTICS, MICROSCOPY, ELECTRON SCANNING*

- ** R01DE-05351-02 Electron optical examination of mineralized tissues (animals)

OPTICS, MICROSCOPY, PHASE*

- ** N01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)

OPTICS, PHOTOGRAPHY*

- SEE ALSO RADIOGRAPHY*
- R01DE-04990-03 Normal and abnormal faces (human)

OPTICS, PHOTOGRAPHY, HOLOGRAPHY*

- SEE ALSO COMPUTER, OPTICAL DATA STORAGE
- R01DE-05495-02 Myofibroblast contraction in periodontium (rats)

OPTICS, PHOTOGRAPHY, STEREOGRAPHY*

- ** R01DE-05582-01 Computer graphic analysis of cranio-facial morphology

ORAL ADMINISTRATION

- SEE DOSAGE AND ROUTE, ROUTE OF ADMINISTRATION

ORAL BEHAVIOR

- SEE DENTISTRY, BRUXISM

ORAL BIOLOGY AND MEDICINE STUDY SECTION

- ** R01DE-01554-20 Host factors in caries resistance (human, rats)
- ** R01DE-01830-19 Quantitation of enamel demineralization mechanisms (human)
- ** R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
- ** R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)
- ** R01DE-02320-16 Clinical behavior of dental restorative materials
- ** R01DE-02525-16 Ultrastructural histopathology of human dental enamel
- ** R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)
- ** R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
- ** R01DE-02936-13 Marginal fracture of dental amalgam
- ** R01DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)
- ** R01DE-03223-11 Kinetics of mineralization of teeth (human)
- ** R01DE-03258-10 Streptococcus mutans--Dental caries mechanism (human)
- ** R01DE-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)
- ** R01DE-03420-09 Immune phenomena in experimental periodontal disease (rats)
- ** R01DE-03488-10 Microbial composition of developing dental plaque
- ** R01DE-03545-09 Prediction of tooth displacement (human)
- ** R01DE-03598-07 Dentofacial effects of forces to retract the maxilla (human)
- ** R01DE-03601-09 Localized corrosion of dental amalgam
- ** R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)
- ** R01DE-03654-09 Molecular basis of dental caries (human)
- ** R01DE-03666-07 X-ray therapeutic index for salivary glands
- ** R01DE-03703-05 Integrated three-dimensional craniofacial measurement (human)
- ** R01DE-03713-06 Effect of fissure sealant on progress of dental caries (human)
- ** R01DE-03739-09 Glycosyltransferases from oral bacteria (bacteria)
- ** R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)
- ** R01DE-03758-07 Virulence characterization and immunization against S mutans (rats, rabbits)
- ** R01DE-03780-09 Permeability characteristics of dentin (dogs, human)

(contd).

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**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number

- ** R01DE-03794-09 Surgical-orthodontics and bone healing (monkeys)
- ** R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)
- ** R01DE-03856-07 Fluoride-selenium interaction in dental caries (rats)
- ** R01DE-03915-08 Tooth-saliva interface phenomena and dental caries (rabbits, goats)
- ** R01DE-03934-07 Differentiation of oral epithelium (rats)
- ** R01DE-03953-07 Force systems from orthodontic appliances
- ** R01DE-03965-08 Dental alloy with small additions of other materials
- ** R01DE-03987-07 Gingival collagen metabolism in health and disease (human, rats)
- ** R01DE-03993-07 Effect of saliva on the metabolism of dental plaque
- ** R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)
- ** R01DE-04047-05 Extensibility characteristics of human cheek
- ** R01DE-04061-07 Salivary antibodies to S mutants--Induction and effects (monkeys)
- ** R01DE-04096-05 Biocompatibility of endodontic materials (animals)
- ** R01DE-04101-07 Corrosion of precious metal alloys (human)
- ** R01DE-04125-06 Gingival matrix proteins and periodontal disease (human, mammals)
- ** R01DE-04136-07 Maxillofacial materials--Color study
- ** R01DE-04141-07 Mechanism of hard tissue mineralization (human, rats)
- ** R01DE-04157-08 Functional mandibular movements (human)
- ** R01DE-04164-06 Functional properties of mammalian masticatory muscles
- ** R01DE-04174-07 Variations in the surface structures of oral bacteria
- ** R01DE-04175-07 Variations in the surface structures of oral bacteria
- ** R01DE-04192-07 SnF₂-Ca (OH) 2-H₃O₄-H₂O reaction system
- ** R01DE-04217-07 Effective immunity to dental caries--Cellular basis
- ** R01DE-04227-07 Adaptations to changes in masticatory muscle length (monkeys)
- ** R01DE-04230-07 Comparative ultrastructure of mammalian amelogenesis (human, mammals)
- ** R01DE-04262-07 Amalgamation kinetics on Ag-Sn (X) alloys
- ** R01DE-04278-06 Human saliva-streptococcal metabolic interactions
- ** R01DE-04296-07 Lysozyme--Cell surface interactions and oral defense
- ** R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
- ** R01DE-04335-05 Comparison of treatment procedures used in endodontics
- ** R01DE-04345-06 Cellular and molecular aspects of mineralization (chick embryo)
- ** R01DE-04385-06 Mechanism of dental caries (human)
- ** R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism
- ** R01DE-04394-05 Pin and slot retention in amalgam and composite materials
- ** R01DE-04414-06 Porous high density polyethylene tooth roots (monkeys)
- ** R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
- ** R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)
- ** R01DE-04486-04 Kinetics and mechanisms of action of fluorides
- ** R01DE-04487-05 Pulsating forces in orthodontics (human)
- ** R01DE-04489-06 Tooth transplantation genetics and immunology (mice, monkeys)
- ** R01DE-04501-06 Cell mediated immunity in gingival inflammation (mice)
- ** R01DE-04504-03 Plaque bacteria as predictors of human dental caries
- ** R01DE-04511-06 Stability of differentiation--Craniofacial study (human, hamsters)
- ** R01DE-04516-03 Corrosion and clinical behavior of dental amalgam
- ** R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate
- ** R01DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins
- ** R01DE-04529-05 Replacement therapy of dental caries (rats, monkeys)
- ** R01DE-04531-04 Strain in the facial bones of (primates)
- ** R01DE-04600-04 Hydroxyapatite remineralization--Role of fluoride
- ** R01DE-04610-03 Physiological studies on mastication (human)
- ** R01DE-04614-05 Adherence of oral streptococci to hydroxyapatite
- ** R01DE-04615-04 Fluoride-cadmium interaction in dental caries (rats, human)
- ** R01DE-04616-04 Fluoride-cadmium interaction in dental caries (rats)
- ** R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)
- ** R01DE-04704-05 X-ray and sem analysis of CU rich dental amalgam
- ** R01DE-04705-03 Reactions of titanium fluoride with hydroxyapatite
- ** R01DE-04721-04 Molecular taxonomy of potential periodontal pathogens (human, monkeys, dogs)
- ** R01DE-04744-04 New antimicrobial agents for preventing oral diseases
- ** R01DE-04779-04 Behavioral stages for cleft palate patients
- ** R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years
- ** R01DE-04795-05 Characteristics of cariogenic dental plaque
- ** R01DE-04814-02 New polymers for permanent soft denture liners
- ** R01DE-04819-05 Remineralization of enamel caries in vitro (human)
- ** R01DE-04835-03 Anti-caries mechanism of fluoride complexes in vitro (human)
- ** R01DE-04844-04 Stress-related bone resorption--Mechanisms of action (rats)
- ** R01DE-04857-02 Temporalis flaps in the treatment of facial paralysis (monkeys)
- ** R01DE-04889-04 Dental significance of jaw muscle silent periods (human)
- ** R01DE-04890-03 Plaque control-healing following periodontal surgery
- ** R01DE-04897-02 Functional development of salivary glands (rats)
- ** R01DE-04903-03 Trace metal uptake in cariogenic streptococcus mutans
- ** R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- ** R01DE-04940-04 Muscular disorders in craniofacial malformations (human)
- ** R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)
- ** R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine
- ** R01DE-04971-03 Human salivary antigens--Characterization (monkeys)
- ** R01DE-05017-03 Characterization of surface antigens of S mutans
- ** R01DE-05024-03 Craniofacial abnormalities in mice with vitamin D resistant rickets
- ** R01DE-05027-04 Binding of fluoride by cariogenic bacteria
- ** R23DE-05036-03 Nocturnal masseter muscle activity and jaw dysfunction (human)
- ** R23DE-05037-03 Biochemical role of zinc in teeth and bones
- ** R23DE-05042-03 Assessment of wear of four different sealants in vivo (human)
- ** R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
- ** R23DE-05050-02 Sources of toxins from human dental plaque
- ** R01DE-05054-03 Periodontal diseases--Microbiological studies
- ** R23DE-05062-03 Tissue interactions during odontogenesis
- ** R23DE-05072-03 Stimulation of regenerating rat submandibular glands
- ** R01DE-05092-03 Proteins involved in dentinogenesis
- ** R01DE-05104-02 Periodontitis--Microbial etiology and prediction
- ** R01DE-05109-02 Composite bone grafts in dentistry and medicine
- ** R01DE-05129-04 Improvement of preventive and restorative materials
- ** R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)
- ** R01DE-05137-03 Microscopic and clinical study of cervical erosion
- ** R01DE-05138-03 Visceral arches and oro-facial morphogenesis (mice, monkeys)
- ** R01DE-05141-03 Cariogenic mechanisms of gingival plaque bacteria
- ** R23DE-05142-03 Control mechanisms in salivary gland development (rats)
- ** R01DE-05145-03 Adjustive cranial skeletal growth (rats)
- ** R23DE-05155-02 Active principles of dental pulp therapeutic agents
- ** R01DE-05156-03 Immunoidentification of periodontal plaque bacteria
- ** R01DE-05159-03 Distribution and ultrastructure of dental innervation (cats)
- ** R01DE-05180-03 Composition of S mutans in different growth environments
- ** R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)
- ** R01DE-05190-03 Factors determining variation in adult oral mucosa
- ** R01DE-05215-03 Influences on stability following orthognathic surgery
- ** R01DE-05224-01 Enamel silylation as a caries prevention method (human, animals)
- ** R23DE-05232-03 Growth and function of the muscles of mastication (monkeys)
- ** R23DE-05240-03 Immunological studies--Caries and periodontal disease (mice)
- ** R01DE-05252-01 Bidirectional effects of subgingival dental plaque
- ** R01DE-05255-03 Regulation of collagenase and bone resorption (chick embryos, mice)
- ** R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)
- ** R01DE-05289-03 Fluorine ion binding by early enamel matrix proteins (rats)
- ** R01DE-05307-03 Orthodontic treatment with removable appliances (human, monkeys)
- ** R23DE-05310-03 Neural control of mandibular movement
- ** R23DE-05314-03 Dental alloy corrosion research
- ** R23DE-05316-03 Salivary calcium binding proteins and oral disease
- ** R01DE-05321-02 Titanium alloys in dentistry
- ** R01DE-05323-02 Calcium transport in developing dental tissues (frogs, rats)
- ** R01DE-05327-03 Polymeric polyphosphonates on dental caries and plaque (rats)
- ** R01DE-05330-02 Herpes virus antibodies in patients with oral cancer
- ** R23DE-05331-01 Local host mechanism in periodontal disease (human, monkeys)
- ** R23DE-05332-03 Bone in vitro--Ultrastructure and autoradiography (mice)
- ** R01DE-05334-02 Periodontal therapy by controlled local drug delivery (human)
- ** R01DE-05352-03 Immunochemical studies in periodontal disease
- ** R01DE-05353-04 Dental porcelains improvement with inorganic polymers
- ** R01DE-05354-04 Prevention of dental caries (rats, human)
- ** R01DE-05359-01 Regulation of secretory immunity to S mutans (mice)
- ** R01DE-05375-01 Surface composition of biological apatites
- ** R01DE-05379-01 Morphogenesis and maturation of craniofacial sutures (animals)
- ** R01DE-05381-01 Temporomandibular joint changes in young adults
- ** R23DE-05393-03 Factors association with hyperplasia of oral mucosa
- ** R01DE-05395-02 Stem cells in oral mucosa
- ** R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)
- ** R01DE-05397-01 Craniofacial bone formation and muscle activity (Rhesus monkey)
- ** R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis (cats)
- ** R01DE-05410-02 Orthodontic treatment effects on craniofacial growth (human)
- ** R01DE-05412-02 Electric current, bone remodeling and tooth movement (cats)
- ** R01DE-05413-02 Bone resorption in periodontal disease
- ** R01DE-05414-02 The local immune response in periodontal disease (human)
- ** R23DE-05418-03 In vivo forces on endosseous dental implants (dogs)
- ** R01DE-05423-02 Diffuse reflectance by esthetic dental materials
- ** R23DE-05424-03 Quantitative studies of lysosomes in amelogenesis (rats)
- ** R01DE-05427-01 Adherence mechanisms of oral microbes
- ** R23DE-05429-03 Adherence of periodontal disease-associated bacteria
- ** R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence
- ** R01DE-05441-02 Optimization of metal-ceramic restoration design
- ** R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)
- ** R01DE-05459-02 Phenytoin--Pathogenesis of gingival overgrowth (cats)
- ** R01DE-05460-02 Bonding of dental porcelain to non-precious alloys
- ** R01DE-05462-01 Saliva mediated aggregation of oral bacteria (human)
- ** R01DE-05483-02 Characterization of predentinal extracellular fluid (rats)
- ** R01DE-05487-02 Kinetics of mineral recycling in teeth and bone
- ** R23DE-05491-02 Control of biomineralization in two species (snails)
- ** R01DE-05494-02 Activation of macrophages in periodontal disease
- ** R01DE-05495-02 Myofibroblast contraction in periodontium (rats)
- ** R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
- ** R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)
- ** R01DE-05510-02 Physico-chemistry of strontium in caries lesions
- ** R01DE-05512-02 Role of macrophages in periodontal disease
- ** R23DE-05519-02 Oxidation behavior of Ni-base crown and bridge alloys
- ** R01DE-05525-02 Nature of the permeability barrier in oral epithelium
- ** R01DE-05530-01 Internal structure of dentine (human, rats)
- ** R01DE-05531-03 Salivary immune factors (human, bacteria)
- ** R23DE-05540-03 Condyllectomy and anterior positioning of the mandible
- ** R01DE-05542-03 Stability of orthognathic surgical procedures (monkeys)
- ** R01DE-05558-01 Sensory alterations of craniofacial form (Rhesus monkeys)
- ** R01DE-05560-01 Rapid identification of oral bacteria
- ** R01DE-05563-02 The blade implant--Clinical efficacy and safety (human)
- ** R01DE-05574-01 Neural aspects of craniofacial morphogenesis (frogs)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

(contd).

- ** R01DE-05582-01 Computer graphic analysis of cranio-facial morphology
- ** R01DE-05586-01 Cell surface studies of the enamel organ (mice)
- ** R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)
- ** R01DE-05596-02 Topically-applied polymers for caries prevention
- ** R23DE-05599-02 Microbiology of ligature-induced periodontitis
- ** R23DE-05605-01 The humoral regulation of pulp circulation (rats)
- ** R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
- ** R01DE-05626-01 Role of complement in periodontal disease
- ** R23DE-05627-02 Effects of mechanical forces on craniofacial growth (monkeys, rabbits)
- ** R01DE-05632-01 Development of salivary gland secretory function (rats)
- ** R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)
- ** R01DE-05634-01 Antibiotic resistance transfer in oral streptococci (human)
- ** R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)
- ** R01DE-05637-01 Mechanical properties of dental composite materials
- ** R01DE-05640-01 Cytotoxicity of periodontopathic bacteria
- ** R01DE-05652-01 Biological role of lysozyme in human saliva
- ** R01DE-05659-01 Surgical and radiographic evaluation of the temporomandibular joint (human)
- ** R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)
- ** R01DE-05669-01 Chorion type and dental morphology in twins
- ** R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs
- ** R01DE-05679-01 Pathophysiology of MPD and other facial pain syndromes (animals)
- ** R01DE-05684-01 Saliva proteins—Chemistry, genetics and oral health
- ** R01DE-05690-01 Localization of the procollagens in dental tissues
- ** R01DE-05698-01 Evaluation of orthognathic surgery patients
- ** R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
- ** R01DE-05728-01 Role of chemoreceptors in craniofacial function (lambs)
- ** R01DE-05729-01 Etiological mechanisms in periodontal disease
- ** R01DE-05732-02 Specificity of cell mediated immune response in periodontal disease
- ** R01DE-05738-01 Mastication, food transport, and swallowing in primates
- ** R01DE-05747-01 Monoclonal antibody analysis of s. mutans antigens
- ** R23DE-05749-01 Salivary proline-rich proteins—Localization/secretion (monkeys)
- ** R01DE-05758-01 Genetic linkage study of cleft lip-palate in Denmark
- ** R01DE-05761-02 Improved dental instruments and materials
- ** R01DE-05769-03 Ultrastructure of tooth development
- ** R01DE-05771-01 Quantitative dental traits in man—Major gene effects
- ** R01DE-05773-01 Ligand receptor interactions of cariogenic bacteria
- ** R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)
- ** R01DE-05800-01 Formation and biochemical composition of sea mussel
- ** R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
- ** R01DE-05817-01 Gingival collagenase—Quantitation and localization (rabbits, mice, human)
- ** R01DE-05832-01 Organization of the trigeminal mesencephalic nucleus (monkeys, opossums)
- ** R01DE-05868-01 Multivariate analysis of craniofacial growth in clefting
- ** R23DE-05883-01 Implants as anchors to move teeth and facial bones (dogs, monkeys)
- ** R23DE-05886-01 Organic oligomers for new hydrophobic dental cements
- ** R23DE-05887-01 Effects of oral bacteria on epithelium in vitro
- ** R13DE-05897-01 Oral immunogenetics and tissue transplantation (symposium)
- ** R23DE-05942-01 Airway factors in cleft palate dentofacial deformity
- ** R23DE-05945-01 Physicochemical modifications of dental restoratives
- ** R23DE-05951-01 Selective microbial ecology of periodontosis siblings
- ** R23DE-05967-01 Role of prostaglandin E in periodontal disease activity
- ** R23DE-05985-01 Growth factors in salivary secretions
- ** R01DE-05991-01 Mechanisms of virulence of oral periodontopathogens
- ** R01DE-05996-01 Alveolar bone metabolism during tooth eruption (Dogs)
- ** R01DE-06000-01 Effect of parotid function on saliva and cells
- ** R01DE-06070-01 Antibiotic susceptibilities of periodontal bacteria

- ** R01DE-06112-01 Filled sealant as a conservative restorative material (human)
- ** R01DE-06113-01 Determinants of fluoride in the oral environment (Dogs, rats)

ORAL-FACIAL-CRANIAL ANOMALIES

SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL

ORAL DISORDERS DIAGNOSIS

SEE ORAL-PHARYNGEAL DISORDERS DIAGNOSIS (INCL EXAMS)*

ORAL-FACIAL PAIN

- SEE ALSO DENTAL PAIN
- SEE ALSO NERVOUS DISORDERS PERIPHERAL, TRIGEMINAL NEURALGIA
- SEE ALSO ORAL-PHARYNGEAL DISORDERS, MPD SYNDROME
- R01DE-04157-08 Functional mandibular movements (human)
- R01DE-04358-06 Treatment of temporomandibular joint pain
- R01DE-04610-03 Physiological studies on mastication (human)
- ** R01DE-04786-04 Dental and orofacial pain—Brain stem mechanisms (cats)
- ** R01DE-04889-04 Dental significance of jaw muscle silent periods (human)
- M R01DE-05130-03 Dental/orofacial pain—Mechanisms behavior and modulation
- ** R01DE-05130-03 0006 Dental/orofacial pain—Mechanisms behavior and modulation - Acute pain in research and clinical settings
- ** R01DE-05208-03 Mechanism of dental and facial sensation (monkeys)
- ** R01DE-05659-01 Surgical and radiographic evaluation of the temporomandibular joint (human)
- ** R01DE-05679-01 Pathophysiology of MPD and other facial pain syndromes (animals)

ORAL-FACIAL RESTORATION

- SEE ALSO DENTAL TRANSPLANTATION
- SEE ALSO ORAL SURGERY
- P01DE-01697-19 0040 A research program in craniofacial problems - Pattern recognition for reconstruction of nasal capsular anatomy
- ** R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)
- M R01DE-03568-07 Craniofacial anomalies—Etiology and treatment
- P01DE-03568-07 0009 Craniofacial anomalies—Etiology and treatment - Cephalometrics
- ** R01DE-03794-09 Surgical-orthodontics and bone healing (monkeys)
- ** R01DE-04136-07 Maxillofacial materials—Color study
- R01DE-04940-04 Muscular disorders in craniofacial malformations (human)
- R01DE-04990-03 Normal and abnormal faces (human)
- R01DE-05203-03 Speech adaptations to orthognathic surgery (human)
- ** R01DE-05215-03 Influences on stability following orthognathic surgery
- ** R01DE-05371-01 Psychosocial evaluation of craniofacial patients
- ** R01DE-05558-01 Sensory alterations of craniofacial form (Rhesus monkeys)
- R01DE-05659-01 Surgical and radiographic evaluation of the temporomandibular joint (human)
- ** R01DE-05698-01 Evaluation of orthognathic surgery patients
- ** R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)
- ** R01DE-05837-01 0002 Growth, surgical, and speech aspects of cleft palate - Maxillofacial growth (dogs, tamarins)
- P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)
- ** R01DE-05837-01 0004 Growth, surgical, and speech aspects of cleft palate - Surgery (human, animals)
- ** R23DE-05883-01 Implants as anchors to move teeth and facial bones (dogs, monkeys)

ORAL-FACIAL RESTORATION, CLEFT PALATE PROSTHESIS

- SEE ALSO DENTAL PROSTHESIS
- ** P01DE-01697-19 0037 A research program in craniofacial problems - Effects of oronasal fistulae on speech (human)
- P01DE-01697-19 0039 A research program in craniofacial problems - Otitis media and its consequences (human)
- ** P01DE-01697-19 0041 A research program in craniofacial problems
- P01DE-02872-12 0038 Craniofacial dysmorphology - Evaluation of craniofacial surgery
- ** R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate
- P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)
- ** P01DE-05837-01 0004 Growth, surgical, and speech aspects of cleft palate - Surgery (human, animals)
- R01DE-05868-01 Multivariate analysis of craniofacial growth in clefting
- R23DE-05942-01 Airway factors in cleft palate dentofacial deformity

ORAL-FACIAL RESTORATION, PROSTHODONTICS

SEE ALSO DENTAL PROSTHESIS

SEE ALSO DRAL-FACIAL RESTORATION, CLEFT PALATE PROSTHESIS

- ** P01DE-02872-12 0053 Craniofacial dysmorphology - Maxillofacial prosthetics (human)
- ** R01DE-03631-08 Physiological study of speech adaptation (human)
- R01DE-04157-08 Functional mandibular movements (human)

ORAL-FACIAL RESTORATION MATERIALS

- ** R01DE-04136-07 Maxillofacial materials—Color study
- R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate
- R01DE-05637-01 Mechanical properties of dental composite materials
- P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)

ORAL FLORA

SEE MICROBIAL DRAL FLORA

ORAL HEALTH

SEE DENTAL HEALTH (ORAL HEALTH)

ORAL MICROBES

SEE MICROBIAL DRAL FLORA

ORAL-PHARYNGEAL (REGION)

- SEE ALSO DENTAL STRUCTURE
- P50DE-02668-15 0196 Regional dental research center - Cytocchemical demonstration of macromolecules of craniofacial tissue
- ** P01DE-03610-15 0016 Cranio-facial growth and development - Craniofacial shape change and oral development
- ** R01DE-05078-05 Craniofacial growth and remodeling (human)
- R01DE-05109-02 Composite bone grafts in dentistry and medicine
- ** R01DE-05138-03 Visceral arches and oro-facial morphogenesis (mice, monkeys)
- ** R23DE-05627-02 Effects of mechanical forces on craniofacial growth (monkeys, rabbits)

ORAL-PHARYNGEAL, CHEEK

- R01DE-03996-06 Low level irradiation-modification of carcinogenesis
- ** R01DE-04047-05 Extensibility characteristics of human cheek

ORAL-PHARYNGEAL, JAW

- SEE ALSO DENTAL STRUCTURE
- ** P01DE-02872-12 0037 Craniofacial dysmorphology - Natural history of cleft lip and palate—Maxillary arch
- R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
- ** R01DE-03598-07 Dentofacial effects of forces to retract the maxilla (human)
- R01DE-05008-03 Basis of drug induced cleft palate (rats, mice)
- ** R01DE-05215-03 Influences on stability following orthognathic surgery
- ** R01DE-05542-03 Stability of orthognathic surgical procedures (monkeys)

ORAL-PHARYNGEAL, JAW, MANDIBLE

- R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)
- P50DE-02668-15 0214 Regional dental research center - Biology of connective tissue, bones, and teeth - Steroid receptors in craniofacial teratology (mice)
- ** P01DE-02848-11 0003 Biology of connective tissue, bones, and teeth - Mandibular morphogenesis—Embryonic neonatal and postnatal development (mice)
- P01DE-02872-12 0037 Craniofacial dysmorphology - Natural history of cleft lip and palate—Maxillary arch
- P01DE-03568-07 0008 Craniofacial anomalies—Etiology and treatment - Craniofacial growth
- R01DE-03794-09 Surgical-orthodontics and bone healing (monkeys)
- ** R01DE-04157-08 Functional mandibular movements (human)
- ** R01DE-04610-03 Physiological studies on mastication (human)
- R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
- R01DE-05215-03 Influences on stability following orthognathic surgery
- R23DE-05232-03 Growth and function of the muscles of mastication (monkeys)
- R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)
- ** R23DE-05540-03 Condylectomy and anterior positioning of the mandible
- R01DE-05542-03 Stability of orthognathic surgical procedures (monkeys)
- R01DE-05558-01 Sensory alterations of craniofacial form (Rhesus monkeys)
- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
- R01DE-05698-01 Evaluation of orthognathic surgery patients
- R23DE-05883-01 Implants as anchors to move teeth and facial bones (dogs, monkeys)

ORAL-PHARYNGEAL, JAW, MANDIBULAR

- CONDYLE
- P01DE-03610-15 0018 Cranio-facial growth and development

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
 **Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number

- R01DE-04157-08 Functional mandibular movements (human)
R01DE-04610-03 Physiological studies on mastication (human)
- R01DE-05381-01 Temporomandibular joint changes in young adults
- ** R23DE-05540-03 Condylectomy and anterior positioning of the mandible
- ORAL-PHARYNGEAL, JAW, TEMPOROMANDIBULAR JOINT**
P50DE-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)
- ** P01DE-03610-15 0018 Cranio-facial growth and development
- R01DE-04157-08 Functional mandibular movements (human)
R01DE-04358-06 Treatment of temporomandibular joint pain
R01DE-04610-03 Physiological studies on mastication (human)
- R01DE-04889-04 Dental significance of jaw muscle silent periods (human)
- R23DE-05036-03 Nocturnal masseter muscle activity and jaw dysfunction (human)
- ** R01DE-05381-01 Temporomandibular joint changes in young adults
- R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)
- ** R01DE-05659-01 Surgical and radiographic evaluation of the temporomandibular joint (human)
- R01DE-05679-01 Pathophysiology of MPD and other facial pain syndromes (animals)
- R01DE-05832-01 Organization of the trigeminal mesencephalic nucleus (monkeys, opossums)
- ORAL-PHARYNGEAL, JAW MOVEMENT**
SEE ALSO DENTISTRY, MASTICATION
- ** P50DE-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)
- R01DE-03631-08 Physiological study of speech adaptation (human)
- ** R01DE-04157-08 Functional mandibular movements (human)
R01DE-04164-06 Functional properties of mammalian masticatory muscles
- R01DE-04610-03 Physiological studies on mastication (human)
- ** R01DE-04884-13 Neural processes in somatic movement (monkeys)
- ** R01DE-04889-04 Dental significance of jaw muscle silent periods (human)
- ** R23DE-05036-03 Nocturnal masseter muscle activity and jaw dysfunction (human)
- ** R23DE-05310-03 Neural control of mandibular movement
- ** R01DE-05738-01 Mastication, food transport, and swallowing in primates
- ORAL-PHARYNGEAL, LIPS**
R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
- R01DE-05213-03 Influences on stability following orthognathic surgery
- ** R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)
- P01DE-05837-01 0004 Grwth, surgical, and speech aspects of cleft palate - Surgery (human, animals)
- ORAL-PHARYNGEAL, MOUTH**
SEE ALSO ORAL-PHARYNGEAL DISORDERS, STOMATITIS
- ** P50DE-02600-15 0032 Support for oral biology research center - Keratohyalin in keratinization of oral mucosa and skin (human, rats)
- P50DE-02668-15 0196 Regional dental research center - Cytochemical demonstration of macromolecules of craniofacial tissue
- ** P50DE-02668-15 0197 Regional dental research center - Peripheral nerves of the orofacial region
- ** P50DE-02731-15 0038 Development support for dental research institute - Antiviral chemotherapy-Drug delivery component
- ** R01DE-03934-07 Differentiation of oral epithelium (rats)
R01DE-04224-07 Genetics of oral microflora
R01DE-05190-03 Factors determining variation in adult oral mucosa
- R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)
- ** R01DE-05525-02 Nature of the permeability barrier in oral epithelium
- ** R01DE-05690-01 Localization of the procollagens in dental tissues
- R01DE-05999-01 The role of nutrition in oral health
- ** R01DE-06113-01 Determinants of fluoride in the oral environment (Dogs, rats)
- ORAL-PHARYNGEAL, MUCOSA**
** P50DE-02600-15 0034 Support for oral biology research center - Salivary and oral mucosal changes after cancer chemotherapy
- R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)
- M P01DE-02848-11 Biology of connective tissue, bones, and teeth
- R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)
- ** R01DE-03934-07 Differentiation of oral epithelium (rats)

- ** R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)
- R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)
- ** R01DE-04660-06 Keratohyalin in keratinization-Oral mucosa and skin (human)
- ** R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
- ** R01DE-05190-03 Factors determining variation in adult oral mucosa
- R01DE-05367-02 Cranio-facial anomalies in the oel mouse
- ** R01DE-05395-02 Stem cells in oral mucosa
- R23DE-05429-03 Adherence of periodontal disease-associated bacteria
- ** R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)
- ** R01DE-05525-02 Nature of the permeability barrier in oral epithelium
- ** R01DE-05999-01 The role of nutrition in oral health
- ORAL-PHARYNGEAL, NASOPHARYNX**
R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)
- R23DE-05942-01 Airway factors in cleft palate dentofacial deformity

ORAL-PHARYNGEAL, PALATE

SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, PALATOPHARYNGEAL ABNORMALITIES

SEE ALSO ORAL-FACIAL RESTORATION, CLEFT PALATE PROSTHESIS

- R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)
- P01DE-02872-12 0063 Craniofacial dysmorphology - Premature craniofacial synostoses (human)
- R01DE-03631-08 Physiological study of speech adaptation (human)
- R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)
- R01DE-04660-06 Keratohyalin in keratinization-Oral mucosa and skin (human)
- ** R01DE-04731-05 Analysis of primary palate formation (chick embryo)
- R01DE-05525-02 Nature of the permeability barrier in oral epithelium
- ** R01DE-05550-01 Cell death during craniofacial embryogenesis
- ** R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)

ORAL-PHARYNGEAL, PHARYNX

SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, PALATOPHARYNGEAL ABNORMALITIES

- SEE ALSO ORAL-PHARYNGEAL, NASOPHARYNX
- ** P01DE-01697-19 0036 A research program in craniofacial problems - Evaluation of velopharyngeal sphincteric function (human)
- ** P01DE-01697-19 0038 A research program in craniofacial problems - Anatomy of the posterior pharyngeal wall
- P01DE-02872-12 0063 Craniofacial dysmorphology - Premature craniofacial synostoses (human)
- R01DE-05145-03 Adjustive cranial skeletal growth (rats)
- R01DE-05738-01 Mastication, food transport, and swallowing in primates

ORAL-PHARYNGEAL, SALIVA

- ** R01DE-01554-20 Host factors in caries resistance (human, rats)
- R01DE-02110-17 Salivary gland structure and function (rats)
- P50DE-02600-15 0030 Support for oral biology research center - Leukocyte function-Its role in periodontal disease (human)
- ** P50DE-02600-15 0039 Support for oral biology research center - Saliva in abnormal bacterial adherence and colonization (human)
- P50DE-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions
- P01DE-02847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
- R01DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)
- R01DE-03488-10 Microbial composition of developing dental plaque
- ** R01DE-03658-17 Genetic polymorphisms of saliva (human)
- ** R01DE-03915-08 Tooth-saliva interface phenomena and dental caries (rabbits, goats)
- ** R01DE-03993-07 Effect of saliva on the metabolism of dental plaque
- R01DE-04217-07 Effective immunity to dental caries-Cellular basis
- ** R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)
- ** R01DE-04278-06 Human saliva-streptococcal metabolic interactions
- R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism
- ** R01DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins
- R01DE-04795-05 Characteristics of cariogenic dental plaque
- R01DE-04819-05 Remineralization of enamel caries in vitro (human)
- ** R01DE-04971-03 Human salivary antigens-Characterization (monkeys)

- ** R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
- R23DE-05240-03 Immunological studies-Caries and periodontal disease (mice)
- ** R23DE-05316-03 Salivary calcium binding proteins and oral disease
- R01DE-05427-01 Adherence mechanisms of oral microbes
- R23DE-05429-03 Adherence of periodontal disease-associated bacteria
- ** R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence
- ** R01DE-05462-01 Saliva mediated aggregation of oral bacteria (human)
- ** R01DE-05652-01 Biological role of lysozyme in human saliva
- ** R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)
- ** R01DE-05678-02 Salivary changes after cancer chemotherapy
- ** R01DE-05684-01 Saliva proteins-Chemistry, genetics and oral health
- R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
- R01DE-05747-01 Monoclonal antibody analysis of S. mutans antigens
- ** R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)
- R01DE-05773-01 Ligand receptor interactions of cariogenic bacteria
- ** R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)
- ** R23DE-05985-01 Growth factors in salivary secretions
- R01DE-06000-01 Effect of parotid function on saliva and cells
- R01DE-12430-00 Investigation of anticaries vaccine in primates
- ** N01DE-92422-04 Dental plaque and saliva from gastric intubated patients

ORAL-PHARYNGEAL, SALIVARY GLANDS

- R01DE-01554-20 Host factors in caries resistance (human, rats)
- ** R01DE-02110-17 Salivary gland structure and function (rats)
- P50DE-02600-15 0034 Support for oral biology research center - Salivary and oral mucosal changes after cancer chemotherapy
- P50DE-02600-15 0039 Support for oral biology research center - Saliva in abnormal bacterial adherence and colonization (human)
- ** P50DE-02668-15 0211 Regional dental research center - Salivary glands and their innervation in diabetes (mice)
- ** P50DE-02668-15 0213 Regional dental research center - Hormone action is the salivary glands of inbred mice
- P50DE-02670-15 0018 Institute of Dental Research - Structure of human secretory immunoglobulin A
- P50DE-02731-15 0038 Development support for dental research institute - Antiviral chemotherapy-Drug delivery component
- ** R01DE-03666-07 X-ray therapeutic index for salivary glands
- ** R01DE-04061-07 Salivary antibodies to S mutants-Induction and effects (monkeys)
- ** R01DE-04897-02 Functional development of salivary glands (rats)
- ** R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)
- ** R23DE-05142-03 Control mechanisms in salivary gland development (rats)
- ** R01DE-05249-02 Salivary secretion-role of calcium (mice)
- ** R01DE-05251-02 Salivary gland secretory mechanisms (rats)
- R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)
- ** R01DE-05531-03 Salivary immune factors (human, bacteria)
- ** R23DE-05749-01 Salivary proline-rich proteins-Localization/secretion (monkeys)
- R23DE-05985-01 Growth factors in salivary secretions

ORAL-PHARYNGEAL, SALIVARY GLANDS, PAROTID

- R01DE-01554-20 Host factors in caries resistance (human, rats)
- R01DE-02110-17 Salivary gland structure and function (rats)
- R01DE-03658-17 Genetic polymorphisms of saliva (human)
- ** R01DE-03666-07 X-ray therapeutic index for salivary glands
- R01DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins
- R01DE-04897-02 Functional development of salivary glands (rats)
- R01DE-04960-03 Mechanisms of salivary gland development (mice, rats)
- R23DE-05142-03 Control mechanisms in salivary gland development (rats)
- R01DE-05249-02 Salivary secretion-role of calcium (mice)
- R01DE-05251-02 Salivary gland secretory mechanisms (rats)
- ** R23DE-05316-03 Salivary calcium binding proteins and oral disease
- R01DE-05462-01 Saliva mediated aggregation of oral bacteria (human)
- R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)
- R01DE-05652-01 Biological role of lysozyme in human saliva
- R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)
- R01DE-05678-02 Salivary changes after cancer chemotherapy

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

- R01DE-05684-01 Saliva proteins--Chemistry, genetics and oral health
- R23DE-05749-01 Salivary proline-rich proteins--Localization/secretion (monkeys)
- ** R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)
- R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)
- ** R01DE-06000-01 Effect of parotid function on saliva and cells

ORAL-PHARYNGEAL, SALIVARY GLANDS, SUBLINGUAL

- R23DE-05142-03 Control mechanisms in salivary gland development (rats)
- R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)

ORAL-PHARYNGEAL, SALIVARY GLANDS, SUBMANDIBULAR

SEE ALSO GROWTH FACTORS (INCL. ANABOLICS), EPIDERMAL GROWTH FACTOR

- R01DE-01554-20 Host factors in caries resistance (human, rats)
- R01DE-02110-17 Salivary gland structure and function (rats)
- P50DE-02668-15 0211 Regional dental research center - Salivary glands and their innervation in diabetes (mice)
- P50DE-02668-15 0213 Regional dental research center - Hormone action is the salivary glands of inbred mice
- R01DE-04518-06 Streptococcus sanguis receptors for salivary glycoproteins
- R01DE-04897-02 Functional development of salivary glands (rats)
- ** R23DE-05072-03 Stimulation of regenerating rat submandibular glands
- R23DE-05142-03 Control mechanisms in salivary gland development (rats)
- ** R01DE-05632-01 Development of salivary gland secretory function (rats)
- R01DE-05652-01 Biological role of lysozyme in human saliva
- R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)
- R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs
- R23DE-05749-01 Salivary proline-rich proteins--Localization/secretion (monkeys)
- ** R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)

ORAL-PHARYNGEAL, SALIVATION

- ** P50DE-02600-15 0034 Support for oral biology research center - Salivary and oral mucosal changes after cancer chemotherapy
- ** R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)
- ** R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)
- ** R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs
- ** R01DE-06000-01 Effect of parotid function on saliva and cells

ORAL-PHARYNGEAL, TONGUE

- SEE ALSO SENSORY-PERCEPTUAL PROCESSES, TASTE
- R01DE-03631-08 Physiological study of speech adaptation (human)
- R01DE-03934-07 Differentiation of oral epithelium (rats)
- R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
- R01DE-05215-03 Influences on stability following orthognathic surgery
- R01DE-05558-01 Sensory alterations of craniofacial form (Rhesus monkeys)

ORAL-PHARYNGEAL DISORDERS (GENERAL)

SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL

SEE ALSO DENTAL DISORDERS

SEE ALSO NEOPLASMS OF ORAL-PHARYNGEAL STRUCTURES

SEE ALSO ORAL-PHARYNGEAL HYPERPLASIA

SEE ALSO ORAL SURGERY

- ** P50DE-02670-15 0020 Institute of Dental Research - Nutrition-Disease proneness during dental development
- ** R01DE-04039-04 Sex steroid metabolism in oral tissues
- R01DE-04957-03 Bacterial metabolites in oral diseases
- ** R23DE-05036-03 Nocturnal masseter muscle activity and jaw dysfunction (human)
- ** R01DE-05089-03 Oral herpes simplex-An approach to dental therapy (hamsters)
- ** R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)
- R01DE-05531-03 Salivary immune factors (human, bacteria)
- R01DE-05837-01 0004 Growth, surgical, and speech aspects of cleft palate - Surgery (human, animals)

ORAL-PHARYNGEAL DISORDERS, MPD SYNDROME

- R23DE-05036-03 Nocturnal masseter muscle activity and jaw dysfunction (human)
- ** R01DE-05679-01 Pathophysiology of MPD and other facial pain syndromes (animals)

ORAL-PHARYNGEAL DISORDERS, SALIVARY GLAND DISORDERS

- P50DE-02600-15 0039 Support for oral biology research center - Saliva in abnormal bacterial adherence and colonization (human)

- R01DE-05531-03 Salivary immune factors (human, bacteria)
- R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs
- R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

ORAL-PHARYNGEAL DISORDERS, STOMATITIS

- R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

ORAL-PHARYNGEAL DISORDERS, STOMATITIS, APHTHOUS

- R01DE-05330-02 Herpes virus antibodies in patients with oral cancer
- R01DE-05525-02 Nature of the permeability barrier in oral epithelium

ORAL-PHARYNGEAL DISORDERS DIAGNOSIS (INCL EXAMS)*

- SEE ALSO BODY PHYSICAL CHARACTERISTICS, CEPHALOMETRY
- SEE ALSO DENTAL DISORDERS DIAGNOSIS (INCL EXAMS)*
- SEE ALSO DENTAL VISUALIZATION*
- R01DE-05679-01 Pathophysiology of MPD and other facial pain syndromes (animals)
- P01DE-05837-01 0002 Growth, surgical, and speech aspects of cleft palate - Maxillofacial growth (dogs, tamarins)
- P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)
- P01DE-05837-01 0004 Growth, surgical, and speech aspects of cleft palate - Surgery (human, animals)

ORAL-PHARYNGEAL HYPERPLASIA

- SEE ALSO DENTAL DISORDERS, GINGIVAL HYPERPLASIA
- R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
- ** R23DE-05393-03 Factors association with hyperplasia of oral mucosa
- R01DE-05395-02 Stem cells in oral mucosa

ORAL-PHARYNGEAL HYPERPLASIA, LEUKOPLAKIA ORAL

- R01DE-05330-02 Herpes virus antibodies in patients with oral cancer
- R23DE-05393-03 Factors association with hyperplasia of oral mucosa

ORAL-PHARYNGEAL MUCOSA

SEE ORAL-PHARYNGEAL, MUCOSA

ORAL-PHARYNGEAL NEOPLASMS

SEE NEOPLASMS OF ORAL-PHARYNGEAL STRUCTURES

ORAL SURGERY

- SEE ALSO DENTAL EXTRACTION
- SEE ALSO DENTAL TRANSPLANTATION
- SEE ALSO DENTISTRY, ENDODONTICS
- SEE ALSO DENTISTRY, SUBGINGIVAL CURETTAGE
- SEE ALSO ORAL-FACIAL RESTORATION
- P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)
- P50DE-02731-15 0033 Development support for dental research institute - Clinical trials of periodontal therapy
- ** R01DE-03794-09 Surgical-orthodontics and bone healing (monkeys)
- R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate
- ** R01DE-05369-03 Factors affecting dental postoperative pain
- ** R23DE-05540-03 Condylectomy and anterior positioning of the mandible
- ** R01DE-05542-03 Stability of orthognathic surgical procedures (monkeys)
- R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)
- R01DE-05698-01 Evaluation of orthognathic surgery patients
- P01DE-05837-01 0002 Growth, surgical, and speech aspects of cleft palate - Maxillofacial growth (dogs, tamarins)
- R13DE-05897-01 Oral immunogenetics and tissue transplantation (symposium)

ORGAN CULTURE

SEE TISSUE (CELL) CULTURE, ORGAN CULTURE

ORGAN TRANSPLANTATION

SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION

ORGANELLES

SEE CELL COMPONENTS, ORGANELLES

ORGANIC COMPOUNDS (GENERAL)

SEE CHEMICALS (GENERAL), ORGANIC COMPOUNDS (GENERAL)

ORGANIC SYNTHESIS

SEE CHEMICAL SYNTHESIS, DESIGN AND PRODUCTION (GENERAL)

ORIENTATION, BODY POSITION

SEE SENSORY-PERCEPTUAL PROCESSES, PROPRICEPTION

ORNITHINE

SEE DIAMINO ACIDS, ORNITHINE

ORTHODONTICS

SEE DENTISTRY, ORTHODONTICS

ORTHOPEDICS

SEE SKELETAL DISORDERS, ORTHOPEDICS

ORTHOPEDICS AND MUSCULOSKELETAL STUDY SECTION

- SEE ALSO SKELETAL DISORDERS, ORTHOPEDICS
- ** R01DE-05112-03 Muscle activity and control in mastication (mammals, lizards)
- ** R01DE-05292-03 Biological prosthetic attachment (dog)

ORTHOTIC MATERIALS

SEE SKELETAL DISORDERS, ORTHOTIC MATERIALS

OSMOTIC PRESSURE, BODY FLUIDS

SEE BODY FLUID BALANCE, OSMOTIC PRESSURE

OSSIFICATION PATHOGENIC

SEE SKELETAL DISORDERS, OSSIFICATION PATHOLOGIC

OSSIFICATION PHYSIOLOGIC

SEE SKELETAL SYSTEM, BONE DEVELOPMENT, OSSIFICATION NORMAL

OSTEITIS FIBROSA CYSTICA RENAL

SEE KIDNEY DISORDERS, RENAL RICKETS

OSTEOARTHRITIS

SEE SKELETAL DISORDERS, ARTHRITIS, OSTEOARTHRITIS

OSTEOBLASTS

SEE SKELETAL SYSTEM, BONE CELLS, OSTEOBLASTS

OSTEOCALCIN

SEE PROTEINS, CALCIUM BINDING PROTEINS

OSTEOCLAST ACTIVATING FACTOR

SEE HYPERSENSITIVITY, LYMPHOKINES, OSTEOCLAST ACTIVATING FACTOR

OSTEOCLASTS

SEE SKELETAL SYSTEM, BONE CELLS, OSTEOCLASTS

OSTEOCYTES

SEE SKELETAL SYSTEM, BONE CELLS

OSTEODYSTROPHY, RENAL

SEE KIDNEY DISORDERS, RENAL RICKETS

OSTEOGENESIS

SEE SKELETAL SYSTEM, BONE DEVELOPMENT, OSTEOGENESIS

OSTEOGENESIS IMPERFECTA

SEE METABOLIC DISORDERS INBORN, OSTEOGENESIS IMPERFECTA

OSTEOGENIC SARCOMA

SEE NEOPLASMS OF SKELETAL SYSTEM, OSTEOGENIC SARCOMA

OSTEOPETROSIS

SEE METABOLIC DISORDERS INBORN, OSTEOPETROSIS

OSTEOPOROSIS

SEE SKELETAL DISORDERS, BONE METABOLISM, OSTEOPOROSIS

OSTEOSCLEROSIS

SEE METABOLIC DISORDERS INBORN, OSTEOPETROSIS

OTITIS MEDIA

SEE EAR DISORDERS, MIDDLE EAR DISORDERS, OTITIS MEDIA

OUTREACH

SEE HEALTH CARE SERVICES, CASE FINDING AND OUTREACH

OVARY

SEE REPRODUCTIVE SYSTEM FEMALE, OVARY

OVOTRANSFERRIN

SEE ALBUMINS, CONALBUMIN

OXIDANTS

- R01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)

OXIDANTS, ANTIOXIDANTS

- R01DE-05144-03 Periodontal disease--Role of spirochetes (rabbits, human)

OXIDATION

SEE OXIDATION-REDUCTION, OXIDATION

OXIDATION-REDUCTION

- SEE ALSO RESPIRATION INTERNAL
- P50DE-02668-15 0150 Regional dental research center - Polymerization of tooth restorative composite materials
- R01DE-03488-10 Microbial composition of developing dental plaque

OXIDATION-REDUCTION, OXIDATION

- R01DE-04252-07 Semi and nonprecious metal-porcelain systems
- ** R23DE-05519-02 Oxidation behavior of Ni-base crown and bridge alloys

OXIDES, SUPEROXIDE

- R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)
- R23DE-05331-01 Local host mechanism in periodontal disease (human, monkeys)

OXIDIZING AGENTS

SEE OXIDANTS

OXIDOREDUCTASES

- SEE ALSO PEROXIDASES
- R01DE-04039-04 Sex steroid metabolism in oral tissues
- R01DE-05494-02 Activation of macrophages in periodontal disease

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects. See Appendix for investigator's name and Grant Number.

OXIDOREDUCTASES, DEHYDROGENASES

- P50DE-02668-15 0196 Regional dental research center -
Cytochemical demonstration of macromolecules of craniofacial
tissue
R01DE-05640-01 Cytotoxicity of periodontopathic bacteria

**OXIDOREDUCTASES, LACTATE
DEHYDROGENASE**

- R01DE-04529-05 Replacement therapy of dental caries (rats,
monkeys)

**OXIDOREDUCTASES, PROSTAGLANDIN
SYNTHASE**

- R01DE-04629-05 Dental disease and osteoclastic bone
resorption (chick embryo, quail)

**OXIDOREDUCTASES, SORBITOL-XYLITOL
DEHYDROGENASE**

- N01DE-02427-04 Synthesize noncariogenic sweeteners

OXIMES

- R01DE-05466-03 Biochemical studies of a sweetener, SRI
Oxime V (rats, mice, dogs, monkeys)

OXYGEN

- SEE RESPIRATORY GASES, OXYGEN

OXYGEN CONSUMPTION

- SEE RESPIRATORY GAS CONSUMPTION, OXYGEN CONSUMPTION

OXYGEN TENSION

- SEE RESPIRATORY GAS LEVELS, OXYGEN TENSION

OXYGENASES, HYDROXYLASES (GENERAL)

- R01DE-04039-04 Sex steroid metabolism in oral tissues

OZ GENES

- SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND
CONTROL

P

- SEE PHOSPHORUS

PAIN

- SEE SENSORY-PERCEPTUAL PROCESSES, PAIN

PAIN, DENTAL

- SEE DENTAL PAIN

PAIN, ORAL-FACIAL

- SEE ORAL-FACIAL PAIN

PAIN RELIEVING AGENTS

- SEE NEUROPHARMACOLOGICAL AGENTS, ANALGESICS

PAIN TOLERANCE

- SEE SENSORY-PERCEPTUAL PROCESSES, PAIN TOLERANCE

PALATE

- SEE ORAL-PHARYNGEAL, PALATE

PALATE, CLEFT

- SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL,
CLEFT PALATE

PALATOPHARYNGEAL ABNORMALITIES

- SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL,
PALATOPHARYNGEAL ABNORMALITIES

PALLADIUM (COMPOUNDS)

- SEE METALS, HEAVY METALS, PALLADIUM (COMPOUNDS)

PALMITIC ACID

- SEE FATTY ACIDS, PALMITIC ACID

PANCREAS HORMONES, INSULIN

- SEE ALSO CARBOHYDRATES METABOLISM DISORDERS,
DIABETES

- R01DE-05505-02 Periodontitis and host defense in juvenile
diabetes (human)

PANCREATIC CYSTIC FIBROSIS

- SEE METABOLIC DISORDERS INBORN, CYSTIC FIBROSIS

PANCREATOPEPTIDASE E

- SEE PROTEASES AND PEPTIDASES, ELASTASE

PAP

- SEE PLANTS EXTRACTS, POKEWEE EXTRACTS

PARALYSIS FACIAL

- SEE NERVOUS DISORDERS PERIPHERAL, FACIAL PARALYSIS

PARANASAL SINUSES

- SEE NASAL, PARANASAL SINUSES

PARASYMPATHETIC NERVOUS SYSTEM

- SEE NERVOUS SYSTEM AUTONOMIC, PARASYMPATHETIC
NERVOUS SYSTEM

PARASYMPATHOLYTIC AGENTS

- SEE NEUROPHARMACOLOGICAL AGENTS, PARASYMPATHOLYTIC

PARASYMPATHOMIMETIC AGENTS

- SEE NEUROPHARMACOLOGICAL AGENTS,
PARASYMPATHOMIMETIC

**PARATHYROID GLANDS DISORDERS,
HYPERPARATHYROIDISM**

- ** R23DE-05607-02 Cells of alveolar bone during
hyperparathyroidism (rats)

PARATHYROID HORMONES

- ** P01DE-01850-18 0068 Nutritional sources and metabolic
roles of fluoride - Radioimmunoassay of parathyroid hormone
in the rat
P50DE-02668-15 0088 Regional dental research center -
Hypervitaminosis D in lactation
** P50DE-02668-15 0207 Regional dental research center -
Effects of vitamin A and D, PTH, CT on uptake of calcium and
phosphorus in enamel
R01DE-03619-09 Biochemistry of tooth eruption, movement
and resorption (cats)
** R01DE-04008-07 Cellular and developmental control of
calcification (tissue culture)
R01DE-04345-06 Cellular and molecular aspects of
mineralization (chick embryo)
R01DE-04629-05 Dental disease and osteoclastic bone
resorption (chick embryo, quail)
P50DE-04881-05 0004 Center for clinical research in
periodontal diseases - Relation of inflammation mediators to
destructive periodontal diseases
R01DE-05136-03 Osteoclast origin and histogenesis in
periodontium (rats)
R01DE-05188-03 Blood vessel response in periodontal disease
(dogs, rats)
** R01DE-05209-04 Metabolic pathways in bone
R01DE-05210-03 Acid phosphatases in developing bones and
teeth (rats)
R23DE-05332-03 Bone in vitro--Ultrastructure and
autoradiography (mice)
R01DE-05413-02 Bone resorption in periodontal disease
R01DE-05487-02 Kinetics of mineral recycling in teeth and
bone
** R23DE-05607-02 Cells of alveolar bone during
hyperparathyroidism (rats)

PARATHYROIDECTOMY

- P50DE-02668-15 0088 Regional dental research center -
Hypervitaminosis D in lactation

PARENT-CHILD

- SEE FAMILY, PARENT-OFFSPRING

PARENT-OFFSPRING

- SEE FAMILY, PARENT-OFFSPRING

PAROTID GLAND

- SEE ORAL-PHARYNGEAL, SALIVARY GLANDS, PAROTID

PAROTITIS, EPIDEMIC

- SEE VIRUS DISEASES, PARAMYXOVIRIDAE, MUMPS

PARTICLES AND PARTICULATE MATTER

- SEE PHYSICAL PROPERTIES, PARTICLES

PASSIVE IMMUNIZATION

- SEE IMMUNITY, IMMUNIZATION PASSIVE

PASSIVE TRANSPORT

- SEE BIOLOGICAL TRANSPORT, PASSIVE TRANSPORT

PASTEUR EFFECT

- SEE HEXOSES, GLYCOLYSIS

PATHOBIOCHEMISTRY STUDY SECTION

- ** R01DE-01374-21 Matrix component interactions in calcified
tissues (cattle, rats, chickens, h
** R01DE-03301-11 Connective tissue of the periodontium--
Collagen maturation
** R01DE-03318-10 The molecular nature of gingival and
mucosal collagen (rat)
** R01DE-04657-05 Abnormal palatal development induced by
hadacidin (fungi)
** R23DE-05793-01 Degradation of collagen in inflammation
(human gingiva)
** R23DE-05956-01 The adhesive of *Mytilus edulis*

PATHOGENIC DIET

- SEE NUTRITION, DIET PATHOGENIC

PATHOLOGIC PROCESSES

- SEE DISEASES, PATHOLOGIC PROCESSES (NOT CLASSIFIED
ELSEWHERE)

PATHOLOGY MICROSCOPIC

- SEE HISTOPATHOLOGY (GENERAL)*

PATIENT CARE, CANCER PATIENTS

- SEE HEALTH CARE SERVICES, CASE FINDING AND OUTREACH

PATIENT CARE MANAGEMENT

- SEE HEALTH CARE SERVICES, PATIENT CARE MANAGEMENT

PATIENT CARE QUALITY

- SEE HEALTH CARE QUALITY

**PATIENT COMPLIANCE WITH THERAPY
REGIMEN**

- SEE THERAPY COMPLIANCE

PATIENT PROFESSIONAL RELATIONS

- SEE HEALTH CARE SERVICES, PATIENT-PROFESSIONAL
RELATIONS

PATIENT REGISTRIES

- SEE HEALTH RECORD SYSTEMS, PATIENT (DISEASE)
REGISTRIES

PATTERN RECOGNITION (COMPUTER)

- SEE COMPUTER, ARTIFICIAL INTELLIGENCE, PATTERN
RECOGNITION AND CONTROL SYSTEMS

**PATTERN RECOGNITION, COMPUTER (OTHER
THAN IMAGE-WAVESHAPE, OR COMPUTER
SIMULATION OR DIAGNOSIS)**

- SEE COMPUTER, ARTIFICIAL INTELLIGENCE, PATTERN
RECOGNITION AND CONTROL SYSTEMS

PD

- SEE METALS, HEAVY METALS, PALLADIUM (COMPOUNDS)

PEDIATRIC CARE (SERVICES)

- SEE CHILD HEALTH CARE (SERVICES)

PEER GROUPS

- SEE PSYCHOLOGY SOCIAL, GROUP PROCESSES, PEER GROUPS

PELECYPODS

- SEE MOLLUSKS, PELECYPODS*

PEMPHIGUS

- SEE SKIN DISORDERS, PEMPHIGUS

PENICILLIN

- SEE ANTIBIOTICS, PENICILLIN

PENTOSES

- P50DE-02600-15 0040 Support for oral biology research
center - Fate of actinomyces viscosus components within
phagocytic cells

PEPTIDE-POLYPEPTIDE RELEASING FACTORS

- SEE PITUITARY-DIENCEPHALON HORMONES, SOMATOSTATIN

PEPTIDE STRUCTURE

- SEE PROTEINS-PEPTIDES STRUCTURE

PEPTIDES

- SEE ALSO PROTEASES AND PEPTIDASES

- N01DE-02428-04 Synthesis of noncariogenic sweeteners
(mice)

PEPTIDES, ENKEPHALIN

- R01DE-04786-04 Dental and orofacial pain--Brain stem
mechanisms (cats)
R01DE-05390-03 Opiate action on CNS terminals of tooth pulp
fibers (animals)
R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis
(cats)

PEPTIDES, POLYPEPTIDES

- R01DE-04321-07 Cell adherence of dental plaque forming
streptococci (rabbits)
R01DE-05354-04 Prevention of dental caries (rats, human)

**PEPTIDES, VASOACTIVE PEPTIDES,
ANGIOTENSIN II**

- R01DE-05390-03 Opiate action on CNS terminals of tooth pulp
fibers (animals)

**PEPTIDES, VASOACTIVE PEPTIDES,
HYPOTENSIVE PEPTIDES**

- R01DE-05404-03 Dental pain--Trigeminal nucleus caudalis
(cats)

PEPTIDES, VASOACTIVE PEPTIDES, KALLIDIN-9

- R23DE-05605-01 The humoral regulation of pulp circulation
(rats)

**PEPTIDES AS BRAIN PEPTIDES FOR
NEUROTRANSMISSION OR
NEUROMODULATION**

- SEE PANCREAS HORMONES, INSULIN
SEE PEPTIDES, ENKEPHALIN
SEE PEPTIDES, VASOACTIVE PEPTIDES, ANGIOTENSIN II
SEE PEPTIDES, VASOACTIVE PEPTIDES, KALLIDIN-9
SEE PITUITARY-DIENCEPHALON HORMONES, ACTH
SEE PITUITARY-DIENCEPHALON HORMONES, ENDORPHINS
SEE PITUITARY-DIENCEPHALON HORMONES, SOMATOSTATIN

PEPTIDES STRUCTURE

- SEE PROTEINS-PEPTIDES STRUCTURE

PEPTIDES TEMPLATES

- SEE NUCLEIC ACIDS, MRNA

PEPTIDOGLYCANS

- SEE ALSO PROTEOGLYCANS
P50DE-02600-15 0040 Support for oral biology research
center - Fate of actinomyces viscosus components within
phagocytic cells
R01DE-05123-04 Periodontopathic bacteria:chemical-biologic
nature (mammals)

PERCEPTION

- SEE SENSORY-PERCEPTUAL PROCESSES, PERCEPTION

PERFORMANCE, JOB

- SEE OCCUPATIONS, JOB PERFORMANCE

PERIODONTAL DISORDERS

- SEE DENTAL DISORDERS, PERIODONTAL

PERIODONTITIS

- SEE DENTAL DISORDERS, PERIODONTITIS

PERIODONTIUM

- SEE DENTAL STRUCTURE, PERIODONTIUM

PERIOSTEUM

- SEE SKELETAL SYSTEM, BONE, PERIOSTEUM

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

PERIPHERAL NERVES (GENERAL)

SEE NERVOUS SYSTEM, PERIPHERAL NERVES (GENERAL)

PERIPHERAL VASCULAR SYSTEM

SEE CARDIOVASCULAR SYSTEM, PERIPHERAL VASCULAR SYSTEM

PERITONEAL DISORDERS

SEE BODY CAVITY DISORDERS, PERITONEAL

PERITONEAL FLUID

SEE BODY CAVITY DISORDERS, PERITONEAL

PERMANENT TEETH

SEE DENTAL STRUCTURE, TOOTH

PERMEABILITY

SEE BIOLOGICAL TRANSPORT, MEMBRANE PERMEABILITY AND TRANSPORT

SEE CARDIOVASCULAR SYSTEM, ENDOTHELIUM PERMEABILITY

PEROXIDASES

R01DE-01554-20 Host factors in caries resistance (human, rats)

P50DE-02600-15 0030 Support for oral biology research center - Leukocyte function--Its role in periodontal disease (human)

R01DE-05632-01 Development of salivary gland secretory function (rats)

R01DE-05684-01 Saliva proteins--Chemistry, genetics and oral health

PEROXIDASES, LACTOPEROXIDASE

R01DE-01554-20 Host factors in caries resistance (human, rats)

** R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)

R01DE-05531-03 Salivary immune factors (human, bacteria)

R01DE-05652-01 Biological role of lysozyme in human saliva

R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora

PEROXIDES

R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)

PERSANTINE

SEE DIAZINODIAZINES, DIPYRIDAMOLE

PERSONAL SATISFACTION

SEE PSYCHOLOGY, ATTITUDES, PERSONAL SATISFACTION

PERSONALITY

SEE PSYCHOLOGY, PERSONALITY

PGA, PROSTAGLANDIN A

SEE FATTY ACIDS, UNSATURATED, PROSTAGLANDINS

PGD, PROSTAGLANDIN D

SEE FATTY ACIDS, UNSATURATED, PROSTAGLANDINS

PGH2, PROSTAGLANDIN H

SEE FATTY ACIDS, UNSATURATED, PROSTAGLANDINS

PH

SEE BODY FLUID BALANCE, ACID-BASE

PH (HYDROGEN ION CONCENTRATION)

SEE ACIDS-BASES, HYDROGEN-ION CONCENTRATION

PHAGE

SEE VIRUSES, BACTERIOPHAGE*

PHAGOCYTES

SEE CELLS, PHAGOCYTES

PHAGOCYTOSIS

SEE CELL INGESTION, PHAGOCYTOSIS

PHARMACOGENETICS

SEE GENETICS, PHARMACOGENETICS*

PHARMACOLOGY

SEE DRUGS, PHARMACOLOGY

PHARMACOLOGY, BIOCHEMICAL

SEE DRUGS, PHARMACOLOGY, BIOCHEMICAL

PHARMACOLOGY STUDY SECTION

** R01DE-05369-04 Factors affecting dental postoperative pain

** R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)

** R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

PHARYNGEAL DISORDERS DIAGNOSIS

SEE ORAL-PHARYNGEAL DISORDERS DIAGNOSIS (INCL EXAMS)*

PHARYNX

SEE ORAL-PHARYNGEAL, PHARYNX

PHASE CHANGE

SEE PHYSICAL PROPERTIES, PHASE CHANGE

PHASE MICROSCOPY

SEE OPTICS, MICROSCOPY, PHASE*

PHASE TRANSITION

SEE PHYSICAL PROPERTIES, PHASE CHANGE

PHENANTHRO(4,5BCD)FURAN-8,9C-IMINOETHANO

SEE ALKALIDS, MORPHINES

PHENOBARBITAL

SEE PYRIMIDINES, BARBITURATES, PHENOBARBITAL

PHENOLIC AMINES, NEOSYNEPHRINE

R01DE-05632-01 Development of salivary gland secretory function (rats)

PHENOLS

R01DE-05327-03 Polymeric polyphosphonates on dental caries and plaque (rats)

R23DE-05886-01 Organic oligomers for new hydrophobic dental cements

PHENOLS, POLYPHENOLSR23DE-05956-01 The adhesive of *Mytilus edulis***PHENOTYPE**

SEE GENETICS, GENES, GENE EXPRESSION

PHENYLALANINE ANALOGS

SEE CYCLIC AMINO ACIDS, PHENYLALANINE ANALOGS

PHENYLALKYLAMINES, CATECHOLAMINES

SEE ALSO CYCLIC AMINO ACIDS, DOPA

SEE ALSO NEUROPHARMACOLOGICAL AGENTS, SYMPATHOMIMETIC

R23DE-05142-03 Control mechanisms in salivary gland development (rats)

PHENYLALKYLAMINES, CATECHOLAMINES, EPINEPHRINE

SEE ALSO NEUROTRANSMITTERS RECEPTORS, ADRENERGIC RECEPTORS

R23DE-05393-03 Factors association with hyperplasia of oral mucosa

PHENYLALKYLAMINES, CATECHOLAMINES, ISOPROTERENOL

R23DE-05072-03 Stimulation of regenerating rat submandibular glands

R23DE-05142-03 Control mechanisms in salivary gland development (rats)

R01DE-05249-02 Salivary secretion-role of calcium (mice)

R01DE-05632-01 Development of salivary gland secretory function (rats)

R01DE-06000-01 Effect of parotid function on saliva and cells

PHENYLALKYLAMINES, CATECHOLAMINES, NOREPINEPHRINE

R01DE-04786-04 Dental and orofacial pain--Brain stem mechanisms (cats)

R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)

R01DE-05632-01 Development of salivary gland secretory function (rats)

R23DE-05633-02 Modulating role of prostaglandins in salivary gland function (rats)

PHENYLAMIDES

R01DE-04744-04 New antimicrobial agents for preventing oral diseases

PHENYLAMIDES, SALICYLAMIDE

R01DE-04744-04 New antimicrobial agents for preventing oral diseases

PHENYL CARBOXYLATES, SALICYLATES

R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)

PHENYL CARBOXYLATES, SALICYLATES, ACETYL-

R01DE-04904-07 Acupuncture and perception of dental pain (human)

R23DE-05393-03 Factors association with hyperplasia of oral mucosa

R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)

R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)

R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

PHENYLEPHRINE

SEE PHENOLIC AMINES, NEOSYNEPHRINE

PHONETICS

SEE INFORMATION-COMMUNICATION BEHAVIOR, SPEECH

PHORBOL

SEE LIPIDS, OILS, CROTON OIL

PHOSPHATASES

SEE ALSO PHOSPHODIESTERASES

R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)

** R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)

PHOSPHATASES, ADENOSINE**TRIPHOSPHATASE**

P50DE-02668-15 0196 Regional dental research center - Cytocchemical demonstration of macromolecules of craniofacial tissue

R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)

R01DE-03469-10 Teratogens effects on cleft palate formation (mice)

R01DE-03715-06 Cellular assembly--Its role in facial morphogenesis (fungi)

R01DE-05586-01 Cell surface studies of the enamel organ (mice)

R01DE-05678-02 Salivary changes after cancer chemotherapeutic drugs

PHOSPHATE DIABETES

SEE METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN

PHOSPHATES

SEE ALSO CALCIUM PHOSPHATES

SEE ALSO NUCLEOTIDES

R01DE-01830-19 Quantitation of enamel demineralization mechanisms

R01DE-01912-18 Tooth enamel apatite at the atomic level (human)

P50DE-02668-15 0193 Regional dental research center - Metabolism of isolated ameloblasts

P50DE-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions

R01DE-03915-08 Tooth-saliva interface phenomena and dental caries (rabbits, goats)

R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

R01DE-05289-03 Fluorine ion binding by early enamel matrix proteins (rats)

R01DE-05354-04 Prevention of dental caries (rats, human)

R01DE-05483-02 Characterization of predentin extracellular fluid (rats)

R01DE-05510-02 Physico-chemistry of strontium in caries lesions

N01DE-12434-00 Identify cariogenic elements of food

PHOSPHATIDES

SEE PHOSPHOLIPIDS

PHOSPHATURIA

SEE CALCIUM (MINERAL) IMBALANCES, PHOSPHORUS IMBALANCE

PHOSPHAZENES

R01DE-04814-02 New polymers for permanent soft denture liners

PHOSPHODIESTERASE INHIBITORS

SEE ENZYME INHIBITORS, PHOSPHODIESTERASE INHIBITORS

PHOSPHODIESTERASES

SEE ALSO PHOSPHOLIPASE

R01DE-03715-06 Cellular assembly--Its role in facial morphogenesis (fungi)

PHOSPHOLIPASE

P50DE-02623-14 0030 Center for oral health research - Role of mitochondria in the mineralization process (chickens)

PHOSPHOLIPASE, LECITHINASE A

R01DE-04141-07 Mechanism of hard tissue mineralization (human, rats)

R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)

R23DE-05332-03 Bone in vitro--Ultrastructure and autoradiography (mice)

PHOSPHOLIPASE A

SEE PHOSPHOLIPASE, LECITHINASE A

PHOSPHOLIPIDS

P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin

R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)

R01DE-04141-07 Mechanism of hard tissue mineralization (human, rats)

R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues

R01DE-05483-02 Characterization of predentin extracellular fluid (rats)

R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)

R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)

R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

PHOSPHOMONOESTERASES, ACID**PHOSPHATASE**

P01DE-01850-18 0081 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on strain N mice

R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)

PHOSPHOMONOESTERASES, ALKALINE**PHOSPHATASE**

P01DE-01850-18 0081 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on strain N mice

** P01DE-01850-18 0086 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on serum alkaline phosphatase activity (mice)

R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)

R01DE-04141-07 Mechanism of hard tissue mineralization (human, rats)

R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)

PHOSPHONATES

P50DE-02670-15 0014 Institute of Dental Research - Mechanism of production of carious lesions

(contd)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

- ** R01DE-05327-03 Polymeric polyphosphonates on dental caries and plaque (rats)
 R01DE-05596-02 Topically-applied polymers for caries prevention

PHOSPHONATES, DIPHOSPHONATES

- R01DE-01830-19 Quantitation of enamel demineralization mechanisms
 R01DE-05327-03 Polymeric polyphosphonates on dental caries and plaque (rats)
 R01DE-05487-02 Kinetics of mineral recycling in teeth and bone

PHOSPHONITRILES

SEE PHOSPHAZENES

PHOSPHOPROTEINS

- R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
 ** P50DE-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues
 R01DE-05092-03 Proteins involved in dentinogenesis
 R01DE-05483-02 Characterization of predentinal extracellular fluid (rats)
 R13DE-05752-01 Conference on biology of mineralized connective tissues

PHOSPHORINS

- SEE ALSO HALOALKYLAMINES, CYCLOPHOSPHAMIDE
 R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)

PHOSPHORUS

- P50DE-02668-15 0207 Regional dental research center - Effects of vitamin A and D, PTH, CT on uptake of calcium and phosphorus in enamel
 P50DE-02670-15 0020 Institute of Dental Research - Nutrition-Disease proneness during dental development
 R01DE-04385-06 Mechanism of dental caries (human)
 R01DE-04486-04 Kinetics and mechanisms of action of fluorides
 R01DE-05289-03 Fluorine ion binding by early enamel matrix proteins (rats)
 R01DE-05375-01 Surface composition of biological apatites
 N01DE-12430-00 Investigation of anticaries vaccine in primates
 N01DE-12432-00 Caries and enamel fluoride

PHOSPHORUS BALANCE (METABOLISM)

- SEE CALCIUM (MINERAL) BALANCE, PHOSPHORUS BALANCE (METABOLISM)

PHOSPHORUS COMPOUNDS (GENERAL)

- P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel

PHOSPHORUS IMBALANCE

- SEE CALCIUM (MINERAL) IMBALANCES, PHOSPHORUS IMBALANCE

PHOSPHORYLATION

- R01DE-05251-02 Salivary gland secretory mechanisms (rats)
 R01DE-05494-02 Activation of macrophages in periodontal disease

PHOSPHOTRANSFERASES

- R01DE-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)

PHOSPHOTRANSFERASES, ADENOSINE KINASE

- R01DE-03715-06 Cellular assembly-Its role in facial morphogenesis (fungi)

PHOSPHOTRANSFERASES, ATP-PYRUVATE

- PHOSPHOTRANSFERASE
 R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism

PHOTOCHEMISTRY

- P50DE-02668-15 0150 Regional dental research center - Polymerization of tooth restorative composite materials

PHOTOGRAPHY

- SEE OPTICS, PHOTOGRAPHY*

PHOTOPERIODISM

- SEE BIOPERIODICITY, CIRCADIAN RHYTHMS

PHYSICAL AND/OR CHEMICAL AGENTS

- INTERACTION (BIOLOGICAL AND ECOLOGICAL)

- SEE ALSO NEOPLASTIC TRANSFORMATION, CARCINOGENS, COCARTINOGENS

- SEE ALSO RADIATION SENSITIVITY, RADIOSENSITIZERS

- ** P50DE-02623-14 0023 Center for oral health research - Interactions of oral bacteria and polymorphonuclear leukocytes
 ** P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin
 P50DE-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues
 P50DE-02731-15 0035 Development support for dental research institute - Immune regulation in periodontal disease
 ** R01DE-03915-08 Tooth-saliva interface phenomena and dental caries (rabbits, goats)
 ** R01DE-04296-07 Lysozyme-Cell surface interactions and oral defense

- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
 ** R01DE-05049-01 Saliva-complement interactions and oral mucosal defense
 ** R23DE-05062-03 Tissue interactions during odontogenesis
 R23DE-05429-03 Adherence of periodontal disease-associated bacteria
 R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)
 R01DE-05459-02 Phenytin-Pathogenesis of gingival overgrowth (cats)
 ** R01DE-05510-02 Physico-chemistry of strontium in caries lesions
 R01DE-05512-02 Role of macrophages in periodontal disease
 R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
 R01DE-05773-01 Ligand receptor interactions of cariogenic bacteria

PHYSICAL CHANGES IN STATES OF MATTER

- SEE PHYSICAL PROPERTIES, PHASE CHANGE

PHYSICAL PROPERTIES (STATES)(PROCESSES)

- SEE ALSO CHEMICAL STRUCTURE
 SEE ALSO DENTAL MATERIALS, WEAR
 SEE ALSO ENVIRONMENT, STRESS MECHANICAL
 SEE ALSO MOLECULAR WEIGHT
 SEE ALSO TEMPERATURE (SEE ALSO THERM...)
 R01DE-03965-08 Dental alloy with small additions of other materials
 R01DE-04262-07 Amalgamation kinetics on Ag-Sn (X) alloys
 ** R23DE-05956-01 The adhesive of Mytilus edulis

PHYSICAL PROPERTIES, ADHESION

- SEE ALSO CELL ADHESION
 SEE ALSO DENTAL MATERIALS, DENTAL ADHESIVES AND SEALANTS
 SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, AGGLUTINATION REACTION (AGGLUTININ)*
 ** P50DE-02600-15 0039 Support for oral biology research center - Saliva in abnormal bacterial adherence and colonization (human)
 P50DE-02623-14 0014 Center for oral health research - Surface receptors on plaque forming organisms
 R01DE-03488-10 Microbial composition of developing dental plaque
 R01DE-04252-07 Semi and nonprecious metal-porcelain systems
 ** R01DE-04614-05 Adherence of oral streptococci to hydroxyapatite
 ** R01DE-05606-02 Pili of S sanguis and their role in adhesion (human, rabbits)
 ** R23DE-05945-01 Physicochemical modifications of dental restoratives

PHYSICAL PROPERTIES, COLLOIDS, SOLS

- R01DE-05353-04 Dental porcelains improvement with inorganic polymers

PHYSICAL PROPERTIES, CRYSTALS,

CRYSTALLIZATION

- P50DE-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins

PHYSICAL PROPERTIES, DENSITY (SPECIFIC

GRAVITY)

- R23DE-05945-01 Physicochemical modifications of dental restoratives

PHYSICAL PROPERTIES, DIFFUSION

- SEE ALSO BIOLOGICAL TRANSPORT, MEMBRANE PERMEABILITY AND TRANSPORT
 SEE ALSO BIOLOGICAL TRANSPORT, PASSIVE TRANSPORT, DIFFUSION
 SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNODIFFUSION TESTS*
 R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
 ** R01DE-03780-09 Permeability characteristics of dentin (dogs, human)

PHYSICAL PROPERTIES, ELASTICITY

- SEE ALSO PLASTICS, ELASTOMERS
 R01DE-04047-05 Extensibility characteristics of human cheek
 R01DE-05321-02 Titanium alloys in dentistry
 R01DE-05637-01 Mechanical properties of dental composite materials
 R23DE-05945-01 Physicochemical modifications of dental restoratives

PHYSICAL PROPERTIES, FLUID FLOW

- SEE ALSO CARDIOVASCULAR FUNCTION, BLOOD FLOW
 R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

PHYSICAL PROPERTIES, MECHANICAL

PRESSURE

- SEE ALSO PHYSICAL PROPERTIES, TENSILE STRENGTH
 ** R01DE-03953-07 Force systems from orthodontic appliances
 ** R01DE-04487-05 Pulsating forces in orthodontics (human)
 ** R23DE-05627-02 Effects of mechanical forces on craniofacial growth (monkeys, rabbits)
 ** R01DE-05637-01 Mechanical properties of dental composite materials

PHYSICAL PROPERTIES, MECHANICAL

VIBRATIONS

- SEE ALSO PHYSICAL PROPERTIES, SOUND
 R01DE-04487-05 Pulsating forces in orthodontics (human)

PHYSICAL PROPERTIES, PARTICLES

- R01DE-05637-01 Mechanical properties of dental composite materials

PHYSICAL PROPERTIES, PHASE CHANGE

- R23DE-05945-01 Physicochemical modifications of dental restoratives

PHYSICAL PROPERTIES, SOLID STATE,

HARDNESS

- ** R01DE-04101-07 Corrosion of precious metal alloys (human)

PHYSICAL PROPERTIES, SOLUBILITY

- R01DE-02525-16 Ultrastructural histopathology of human dental enamel
 ** R01DE-03187-10 Transport in enamel and solubility of fluoridated apatites (human)
 R23DE-05886-01 Organic oligomers for new hydrophobic dental cements

PHYSICAL PROPERTIES, SOLUBILITY, WATER

- R01DE-05596-02 Topically-applied polymers for caries prevention

PHYSICAL PROPERTIES, SOLVENTS

- R01DE-05525-02 Nature of the permeability barrier in oral epithelium

PHYSICAL PROPERTIES, SOUND

- ** R01DE-05203-03 Speech adaptations to orthognathic surgery (human)

PHYSICAL PROPERTIES, SOUND, ULTRASONIC

SCANNING*

- R01DE-03631-08 Physiological study of speech adaptation (human)

PHYSICAL PROPERTIES, SURFACE PROPERTIES

(GENERAL)

- SEE ALSO MEMBRANE SURFACE (BIOLOGICAL) ACTIVITY (GENERAL)

- ** P01DE-02847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
 R01DE-03497-09 Artificial tooth roots (Rhesus monkeys, human)
 R01DE-04814-02 New polymers for permanent soft denture liners
 R01DE-04819-05 Remineralization of enamel caries in vitro (human)
 R01DE-04835-03 Anti-caries mechanism of fluoride complexes in vitro (human)
 R01DE-04883-04 Nature of alloy systems for crown and bridge restorations (human)
 R01DE-05141-03 Cariogenic mechanisms of gingival plaque bacteria
 ** R01DE-05224-01 Enamel silylation as a caries prevention method (human, animals)
 R01DE-05292-03 Biological prosthetic attachment (dog)
 R01DE-05354-04 Prevention of dental caries (rats, human)
 R23DE-05519-02 Oxidation behavior of Ni-base crown and bridge alloys
 R23DE-05945-01 Physicochemical modifications of dental restoratives

PHYSICAL PROPERTIES, SURFACTANTS

- R01DE-01830-19 Quantitation of enamel demineralization mechanisms
 R01DE-04819-05 Remineralization of enamel caries in vitro (human)
 R01DE-05525-02 Nature of the permeability barrier in oral epithelium
 R23DE-05945-01 Physicochemical modifications of dental restoratives

PHYSICAL PROPERTIES, TENSILE STRENGTH

- SEE ALSO ENVIRONMENT, STRESS MECHANICAL

- ** P50DE-02668-15 0149 Regional dental research center - Strengths of polymers in tooth restorative materials
 R01DE-03953-07 Force systems from orthodontic appliances
 R01DE-04883-04 Nature of alloy systems for crown and bridge restorations (human)
 R01DE-05637-01 Mechanical properties of dental composite materials

PHYSICAL SEPARATION, FRACTIONATION

(GENERAL)*

- R01DE-05637-01 Mechanical properties of dental composite materials

PHYSIOLOGICAL CHEMISTRY STUDY SECTION

- ** R01DE-03578-10 Biosynthetic study of dental plaque polysaccharides
 ** R01DE-03715-06 Cellular assembly-Its role in facial morphogenesis (fungi)
 ** R01DE-03731-06 Dextran sucrose of Streptococcus sanguis

PHYSIOLOGICAL PSYCHOLOGY

- SEE PSYCHOBIOLOGY, PSYCHOLOGY

PHYSIOLOGY (GENERAL)*

- SEE ALSO ELECTROPHYSIOLOGY

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
 **Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

- SEE ALSO MICROBIAL PHYSIOLOGY STUDY SECTION
SEE ALSO NEUROPHYSIOLOGY (GENERAL)
SEE ALSO PSYCHOBIOLOGY, PSYCHOPHYSIOLOGY
- ** R01DE-03631-08 Physiological study of speech adaptation (human)
 - ** R23DE-05809-01 Effects of fluoride on physiology of oral bacteria
 - ** P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)

PHYSIOLOGY STUDY SECTION

- ** R01DE-02110-17 Salivary gland structure and function (rats)

PSYCHOPHYSIOLOGY

- SEE PSYCHOBIOLOGY, PSYCHOPHYSIOLOGY

PHYTOAGGLUTININS

- SEE PLANTS PROTEINS, LECTINS

PHYTOLACCA SP.

- SEE PLANTS, ANGIOSPERMS, POKEWEED*

PHYTOLACCACEAE

- SEE PLANTS, ANGIOSPERMS, POKEWEED*

PHYTOMITOGENS

- SEE PLANTS PROTEINS, LECTINS

PICTORIAL DATA PROCESSING (COMPUTER)

- SEE OPTICS, IMAGE PROCESSING ANALYSIS AND DISPLAY*

PIERRE ROBIN SYNDROME

- SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, PIERRE-ROBIN SYNDROME

PIGEON BERRY

- SEE PLANTS, ANGIOSPERMS, POKEWEED*

PIGMENT CELL NEOPLASMS, MELANOMA

- ** R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

PIGMENTS

- R01DE-04136-07 Maxillofacial materials--Color study

PILI

- SEE CELL COMPONENTS, PILI

PILOCARPINE TYPE ALKALOIDS

- SEE ALKALOIDS, PILOCARPINE TYPE

PINOCYTOSIS

- SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, PINOCYTOSIS

PIPE SMOKING

- SEE PSYCHOLOGY, HABITS, SMOKING

PITUITARY-DIENCEPHALON HORMONES, ACTH

- R01DE-05369-03 Factors affecting dental postoperative pain

PITUITARY-DIENCEPHALON HORMONES, ENDORPHINS

- SEE ALSO NEUROTRANSMITTERS RECEPTORS, ENDORPHIN RECEPTORS
- R01DE-05369-03 Factors affecting dental postoperative pain

PITUITARY-DIENCEPHALON HORMONES, SOMATOSTATIN

- R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)

PLACEBO EFFECT

- SEE THERAPY, PLACEBO EFFECT

PLACENTA

- SEE PREGNANCY, PLACENTA

PLACENTAL BARRIER

- SEE PREGNANCY CIRCULATION, PLACENTAL TRANSFER

PLACENTAL TRANSFER

- SEE PREGNANCY CIRCULATION, PLACENTAL TRANSFER

PLANTS, ANGIOSPERMS, POKEWEED*

- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

PLANTS EXTRACTS, POKEWEED EXTRACTS

- R01DE-05414-02 The local immune response in periodontal disease (human)

PLANTS PROTEINS, LECTINS

- P01DE-02847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
- R01DE-04296-07 Lysozyme--Cell surface interactions and oral defense
- R01DE-05414-02 The local immune response in periodontal disease (human)
- R01DE-05436-03 Salivary proteins in bacterial aggregation/adherence
- R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)

PLANTS PROTEINS, LECTINS, CONCAVALIN A

- R01DE-05414-02 The local immune response in periodontal disease (human)

PLAQUE

- SEE DENTAL DEPOSITS, PLAQUE

PLAQUE REMOVAL

- SEE DENTAL DEPOSITS REMOVAL

PLASMA

- SEE BLOOD AND RE SYSTEM, BLOOD, PLASMA

PLASMA MEMBRANE

- SEE CELL COMPONENTS, CELL MEMBRANE

PLASMA PROTEINS

- SEE BLOOD PROTEINS

PLASMALEMMMA

- SEE CELL COMPONENTS, CELL MEMBRANE

PLASMID CLONING

- SEE NUCLEIC ACIDS CLONING

PLASMIDS

- SEE GENETICS, EXTRACHROMOSOMAL INHERITANCE, PLASMIDS

PLASTIC SURGERY

- SEE SURGERY, PLASTIC

PLASTICS, ACRYLIC POLYMERS

- R01DE-04814-02 New polymers for permanent soft denture liners
- R23DE-05945-01 Physicochemical modifications of dental restoratives

PLASTICS, ACRYLIC POLYMERS, METHACRYLATES

- R23DE-05945-01 Physicochemical modifications of dental restoratives

PLASTICS, ELASTOMERS

- R01DE-04136-07 Maxillofacial materials--Color study
- R01DE-04814-02 New polymers for permanent soft denture liners

PLASTICS, FLUOROCARBON POLYMERS

- P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)

PLASTICS, POLYETHYLENES

- ** R01DE-0414-06 Porous high density polyethylene tooth roots (monkeys)
- R01DE-04814-02 New polymers for permanent soft denture liners

PLASTICS, POLYURETHANES

- R01DE-04814-02 New polymers for permanent soft denture liners

PLASTICS, STYRENE POLYMERS

- R01DE-04814-02 New polymers for permanent soft denture liners

PLATELET ACTIVATING FACTOR

- SEE BLOOD PLATELETS, PLATELET ACTIVATING FACTOR

PLATINUM (COMPOUNDS)

- SEE METALS, HEAVY METALS, PLATINUM (COMPOUNDS)

PLEASURE (EMOTIONS)

- SEE PSYCHOLOGY, EMOTIONS, PLEASURE-DISPLEASURE (GENERAL)

PLEIOTROPISM

- SEE GENETICS, GENES, GENE EXPRESSION, PLEIOTROPISM

PLUMBISM

- SEE METALS POISONING, LEAD POISONING

PMA (PHORBOL MYRISTATE)

- SEE LIPIDS, DILS, CROTON OIL

PODOPHYLLIN

- SEE NAPHTHALENES, METHYLENEDIOLY-, PODOPHYLLIN

PODOPHYLLUM RESIN

- SEE NAPHTHALENES, METHYLENEDIOLY-, PODOPHYLLIN

POKEWEEDS

- SEE PLANTS, ANGIOSPERMS, POKEWEED*

POKEWEED EXTRACTS

- SEE PLANTS EXTRACTS, POKEWEED EXTRACTS

POKEWEED MITOGEN

- SEE PLANTS EXTRACTS, POKEWEED EXTRACTS

POLARIZATION OPTICS

- SEE OPTICAL POLARIZATION*

POLARIZED PUMPING MEMBRANES

- SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS

POLIOMYELITIS LIVE VACCINE

- SEE VACCINES, LIVE

POLIOMYELITIS VIRUS

- SEE VIRUSES, PICORNAVIRIDAE, ENTEROVIRUS, POLIOMYELITIS VIRUS

POLIOVIRUS (HUMAN) 1,2,3

- SEE VIRUSES, PICORNAVIRIDAE, ENTEROVIRUS, POLIOMYELITIS VIRUS

POLYAMINES

- SEE AMINES, POLYAMINES

POLYANIONS

- SEE IONS, POLYIONS, POLYANIONS

POLYCYCLIC HYDROCARBONS

- SEE CYCLICS, CARBOPOLYCYCLICS

POLYETHYLENES

- SEE PLASTICS, POLYETHYLENES

POLYMERIZATION

- SEE MOLECULAR CONDENSATIONS, POLYMERIZATION-DEPOLYMERIZATION

POLYMERS

- SEE MOLECULAR CONDENSATIONS, POLYMERS (GENERAL)

POLYMORPHISM (BIOLOGY)

- SEE BIOLOGY, POLYMORPHISM

POLYMORPHONUCLEAR LEUKOCYTES

- SEE BLOOD CELLS, LEUKOCYTES, NEUTROPHILS

POLYNUCLEOTIDE LIGASE

- SEE NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)

POLYNUCLEOTIDE LIGASE (NAD)

- SEE NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)

POLYNUCLEOTIDE SYNTHETASE (ATP)

- SEE NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)

POLYNUCLEOTIDE SYNTHETASE (NAD)

- SEE NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)

POLYPEPTIDES

- SEE PEPTIDES, POLYPEPTIDES

POLYPHENOLS

- SEE PHENOLS, POLYPHENOLS

POLYSACCHARIDES

- ** R01DE-03118-11 Inhibition of saccharide metabolism by oral flora
- R01DE-04061-07 Salivary antibodies to S mutans--Induction and effects (monkeys)
- R01DE-04224-07 Genetics of oral microflora
- R01DE-05017-03 Characterization of surface antigens of S mutans
- R01DE-05141-03 Cariogenic mechanisms of gingival plaque bacteria

POLYSACCHARIDES, BACTERIAL (GENERAL)

- SEE ALSO IMMUNOLOGY, ANTIGENS BACTERIAL
- SEE ALSO PEPTIDOGLYCANS
- SEE ALSO POLYSACCHARIDES, TEICHOIC ACID
- ** R01DE-03578-10 Biosynthetic study of dental plaque polysaccharides
- R01DE-03654-09 Molecular basis of dental caries (human)
- R01DE-03995-07 Leukocytes in the pathogenesis of periodontal disease (human, mice)
- R01DE-04808-02 Virulence factors of gram negative corroding bacteria
- R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque
- R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)
- R01DE-72408-06 Cross-reacting antigens/oral flora acidogenic bacteria

POLYSACCHARIDES, GLYCOSAMINOGLYCANS

- SEE ALSO METABOLIC DISORDERS INBORN, MUCOPOLYSACCHARIDOSIS, LIPOCHONDRODYSSTROPHY
- SEE ALSO POLYSACCHARIDES, LIPOPOLYSACCHARIDES
- ** P01DE-01850-18 0088 Nutritional sources and metabolic roles of fluoride - Fluoride and glycosaminoglycans in bone (mice)
- P50DE-02670-15 0024 Institute of Dental Research - Metabolism of connective tissue proteoglycans
- P50DE-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues
- R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)
- ** R01DE-04316-05 Extracellular matrix and morphogenesis in mutant mice (also birds)
- R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
- R23DE-05037-03 Biochemical role of zinc in teeth and bones
- R23DE-05062-03 Tissue interactions during odontogenesis
- R01DE-05379-01 Morphogenesis and maturation of craniofacial sutures (animals)
- R01DE-05413-02 Bone resorption in periodontal disease
- R01DE-05630-01 Matrix/cell surface in neural crest cell morphogenesis (mice, chick, quail)
- R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)
- R23DE-05956-01 The adhesive of *Mytilus edulis*

POLYSACCHARIDES, GLYCOSAMINOGLYCANS, CHONDROITIN SULFATE

- ** P50DE-02670-15 0024 Institute of Dental Research - Metabolism of connective tissue proteoglycans
- P50DE-02670-15 0029 Institute of Dental Research - Structure of connective tissue proteoglycans (cattle)

POLYSACCHARIDES, GLYCOSAMINOGLYCANS, HEPARIN

- P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

(contd.)

- ** P50DE-02670-15 0024 Institute of Dental Research - Metabolism of connective tissue proteoglycans
R01DE-05413-02 Bone resorption in periodontal disease

POLYSACCHARIDES, GLYCOSAMINOGLYCANS, HYALURONIC ACID

- P50DE-02670-15 0029 Institute of Dental Research - Structure of connective tissue proteoglycans (cattle)
P50DE-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues
R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)
** R01DE-05838-02 Morphogenetic role of glycosaminoglycans (chick embryo)

POLYSACCHARIDES, LIPOPOLYSACCHARIDES

- SEE ALSO GLYCOLIPIDS
SEE ALSO IMMUNOLOGY, ANTIGENS MICROBIAL, ZYMOSAN
R01DE-04217-07 Effective immunity to dental caries--Cellular basis
** R01DE-04957-03 Bacterial metabolites in oral diseases
R01DE-05123-04 Periodontopathic bacteria: chemical-biologic nature (mammals)
R01DE-05414-02 The local immune response in periodontal disease (human)
R01DE-05494-02 Activation of macrophages in periodontal disease

POLYSACCHARIDES, TEICHOIC ACID

- ** R01DE-04957-03 Bacterial metabolites in oral diseases

POLYSTYRENES

- SEE PLASTICS, STYRENE POLYMERS

POLYTETRAFLUOROETHYLENES

- SEE PLASTICS, FLUOROCARBON POLYMERS

POLYURETHANES

- SEE PLASTICS, POLYURETHANES

POPULATION GENETICS HUMAN

- SEE GENETICS, POPULATION GENETICS HUMAN

POPULATION GENETICS MICROORGANISMS

- SEE GENETICS, POPULATION GENETICS MICROORGANISMS

POPULATION STUDIES ANIMAL, LONGITUDINAL STUDY

- R01DE-03497-09 Artificial tooth roots (Rhesus monkeys, human)

POPULATION STUDIES CELL

- SEE ALSO CELL GROWTH REGULATION

- SEE ALSO CELL MIGRATION

- ** R01DE-04731-05 Analysis of primary palate formation (chick embryo)
R01DE-05395-02 Stem cells in oral mucosa
R01DE-05550-01 Cell death during craniofacial embryogenesis
R01DE-05555-01 Cell migration in the teleost embryo

POPULATION STUDIES HUMAN

- SEE ALSO GENETICS, POPULATION GENETICS HUMAN
P01DE-01850-18 0087 Nutritional sources and metabolic roles of fluoride - Methodology for determining ionic fluoride content of human plasma
** R01DE-05698-01 Evaluation of orthognathic surgery patients

POPULATION STUDIES HUMAN, EPIDEMIOLOGY

- SEE ALSO EPIDEMIOLOGY AND DISEASE CONTROL STUDY SECTION

- ** R23DE-05497-02 Dental disease and work loss (human)

POPULATION STUDIES HUMAN, LONGITUDINAL STUDY

- P01DE-01697-19 0039 A research program in craniofacial problems - Otitis media and its consequences (human)
P01DE-01697-19 0040 A research program in craniofacial problems - Pattern recognition for reconstruction of nasal capsular anatomy
P01DE-01697-19 0041 A research program in craniofacial problems -
R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
P50DE-02668-15 0191 Regional dental research center - Clinical evaluation of restorative materials and techniques
P50DE-02731-15 0035 Development support for dental research institute - Immune regulation in periodontal disease
P01DE-02872-12 0036 Craniofacial dysmorphology - Natural history of cleft lip and palate--Malocclusion
P01DE-02872-12 0038 Craniofacial dysmorphology - Evaluation of craniofacial surgery
R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
M P01DE-03568-07 Craniofacial anomalies--Etiology and treatment
R01DE-04157-08 Functional mandibular movements (human)
R01DE-04278-06 Human saliva-streptococcal metabolic interactions
R01DE-04504-03 Plaque bacteria as predictors of human dental caries
R01DE-04779-04 Behavioral stages for cleft palate patients
R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years
R01DE-04795-05 Characteristics of cariogenic dental plaque

- P50DE-04881-05 0001 Center for clinical research in periodontal diseases - Diagnosis and treatment of destructive periodontal diseases
P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)
P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)
R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)
R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)
R23DE-05331-01 Local host mechanism in periodontal disease (human, monkeys)
R01DE-05371-01 Psychosocial evaluation of craniofacial patients
R01DE-05410-02 Orthodontic treatment effects on craniofacial growth (human)
R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
** R01DE-05511-02 Evanston-Oak park fluoridation study after 25 years (human)
R01DE-05563-02 The blade implant--Clinical efficacy and safety (human)
R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)
** P01DE-05837-01 0001 Growth, surgical, and speech aspects of cleft palate - Speech pathology (human)
P01DE-05837-01 0003 Growth, surgical, and speech aspects of cleft palate - Speech physiology and anatomy (children, adults)
R23DE-05967-01 Role of prostaglandin E in periodontal disease activity
N01DE-12431-00 Clinical trial of a combined MFP-NaF dentifrice
** N01DE-82413-05 Long-term effect of orthodontic treatment
N01DE-82417-03 Effect of daily mouthrinsing with fluorides

POPULATION STUDIES HUMAN, MORBIDITY

- R23DE-05497-02 Dental disease and work loss (human)
R01DE-05563-02 The blade implant--Clinical efficacy and safety (human)

POPULATION STUDIES MICROORGANISMS

- SEE ALSO ENVIRONMENT, ECOLOGY ORGANISMS
SEE ALSO GENETICS, POPULATION GENETICS MICROORGANISMS
SEE ALSO REPRODUCTION MICROORGANISMS
P50DE-02600-15 0037 Support for oral biology research center - Periodontal microflora (human)
R01DE-05606-02 Pili of *S. sanguis* and their role in adhesion (human, rabbits)

POPULATION SURVEYS

- R01DE-05622-01 Rx for dental patients at risk for endocarditis (dentists)
** N01DE-92421-14 National caries prevalence survey

POPULATION SURVEYS, HEALTH SURVEYS, DENTAL

- R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
R23DE-05497-02 Dental disease and work loss (human)
** R01DE-05511-02 Evanston-Oak park fluoridation study after 25 years (human)

PORCELAINS, DENTAL

- SEE DENTAL MATERIALS, PORCELAINS

POST-MORTEM

- SEE DEATH, POST-MORTEM

POSTNATAL

- SEE CHILDREN, INFANT NEWBORN (BIRTH TO 4-6 WKS)

POSTOPERATIVE

- SEE SURGERY, POSTOPERATIVE

POSTOPERATIVE COMPLICATIONS

- SEE DISEASES, COMPLICATIONS, POSTOPERATIVE

POSTURE

- SEE SKELETAL MOVEMENT, POSTURE

POTASSIUM

- R01DE-05354-04 Prevention of dental caries (rats, human)
R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)
R01DE-05483-02 Characterization of predental extracellular fluid (rats)
R23DE-05809-01 Effects of fluoride on physiology of oral bacteria

POTASSIUM PUMP

- SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS, POTASSIUM PUMP

POTENTIALS

- SEE ELECTROPOTENTIALS

POTENTIATION

- SEE DRUGS AND PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION
SEE DRUGS INTERACTION
SEE PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION (BIOLOGICAL AND ECOLOGICAL)

POULTRY PRODUCTS

- SEE FOOD, POULTRY PRODUCTS

PRACTICE IN LEARNING

- SEE PSYCHOLOGY, LEARNING, REHEARSAL

PREDICTION OF DISEASE OUTCOME

- SEE DISEASES, PROGNOSIS

PREDISPOSITION TO DISEASE

- SEE DISEASE PRONENESS-RISK

PREGNANCY, EMBRYO-FETUS

- SEE ALSO EMBRYOLOGY, EARLY EMBRYONIC STAGES (1-28 DAYS)

- SEE ALSO EMBRYOLOGY, EMBRYO-FETAL CELLS AND TISSUES
SEE ALSO GENETICS, DEVELOPMENTAL GENETICS

- ** P01DE-02848-11 0003 Biology of connective tissue, bones, and teeth - Mandibular morphogenesis--Embryonic neonatal and postnatal development (mice)
R01DE-05367-02 Cranio-facial anomalies in the oel mouse (mice)
** R01DE-05379-01 Morphogenesis and maturation of craniofacial sutures (animals)
R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)

PREGNANCY, EMBRYO-FETUS CULTURE

- R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)

PREGNANCY, EMBRYO-FETUS DRUGS

ADVERSE EFFECTS

- SEE ALSO CONGENITAL ABNORMALITIES, DRUG INDUCED
SEE ALSO CONGENITAL ABNORMALITIES, TERATOGENIC AGENTS
SEE ALSO PREGNANCY DISORDERS, EMBRYO-FETAL DISORDERS, FETAL ALCOHOL DISORDERS

- R01DE-03469-10 Teratogens effects on cleft palate formation (mice)
R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)
N01DE-52452-12 Oral facial malformations in the rhesus monkey

PREGNANCY, EMBRYO-FETUS

PHARMACOLOGY

- SEE ALSO PREGNANCY, EMBRYO-FETUS DRUGS ADVERSE EFFECTS

- R01DE-05168-03 Glucocorticoid receptors and cleft palate (mice)

PREGNANCY, EMBRYO-FETUS TOXICOLOGY

- SEE ALSO CONGENITAL ABNORMALITIES, TERATOGENIC AGENTS
SEE ALSO PREGNANCY, EMBRYO-FETUS DRUGS ADVERSE EFFECTS

- R01DE-05041-03 Orofacial anomalies in phenytoin teratogenesis (mice, human)

PREGNANCY, PLACENTA

- ** P50DE-02670-15 0035 Institute of Dental Research - Granulocyte growth and division

PREGNANCY CIRCULATION, PLACENTAL TRANSFER

- SEE ALSO PREGNANCY IMMUNOLOGY

- R01DE-05165-03 Genetic control of susceptibility to cleft palate (mice)

PREGNANCY DISORDERS

- SEE ALSO PREGNANCY, EMBRYO-FETUS DRUGS ADVERSE EFFECTS

- SEE ALSO PREGNANCY, EMBRYO-FETUS TOXICOLOGY

- P50DE-02731-15 0021 Development support for dental research institute - Bacterial specificity in periodontal disease

PREGNANCY DISORDERS, EMBRYO-FETAL DISORDERS, FETAL ALCOHOL DISORDERS

- ** P50DE-02668-15 0212 Regional dental research center - Determination of risk related to alcohol consumption before pregnancy recognition

PREGNANCY DISORDERS, EMBRYO-FETAL GROWTH-DEVELOPMENT DISORDERS (SEE ALSO APPROPRIATE SPECIFICS)

- SEE ALSO CONGENITAL ABNORMALITIES, SKELETAL (GENERAL)

- ** P50DE-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)

- P01DE-02848-11 0002 Biology of connective tissue, bones, and teeth - Steroid receptors in craniofacial teratology (mice)

- P01DE-02848-11 0003 Biology of connective tissue, bones, and teeth - Mandibular morphogenesis--Embryonic neonatal and postnatal development (mice)

- P01DE-03610-15 0017 Cranio-facial growth and development - Craniofacial profile patterns in normal and malformed prenatals and postnatals

- ** R01DE-05078-05 Craniofacial growth and remodeling (human)

PREGNANCY IMMUNOLOGY

- ** R23DE-05006-03 Maternal malnutrition--Pregnancy immunology (human)

PREGNANCY MEMBRANES, CHORION

- ** R01DE-05669-01 Chorion type and dental morphology in twins (contd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level. *

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects. See Appendix for investigator's name and Grant Number.

PREGNANE SERIES SALPHA, SALPHA-PREGNANE-3BETA, 17ALPHA, 21-TRIOL-20-ONE
 R010E-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)

SALPHA-PREGNANE-3BETA, 17ALPHA-21-TRIOL-20-ONE
 SEE PREGNANE SERIES SALPHA, SALPHA-PREGNANE-3BETA, 17ALPHA, 21-TRIOL-20-ONE

PREMATURE INFANT
 SEE CHILDREN, INFANT PREMATURE AND LOW BIRTH WEIGHT

PREOPERATIVE
 SEE SURGERY, PREOPERATIVE

PREPARATION OF BIOMATERIALS
 SEE BIOMATERIALS, DEVELOPMENT AND PREPARATION OF BIOMATERIALS

PRESCHOOL
 SEE CHILDREN, PRESCHOOL (1 TO 6 YRS)

PRESERVATION
 SEE TISSUE (CELL) CULTURE, CELL CULTURE COLLECTIONS BANKS AND REGISTRIES

PRESSURE, BLOOD
 SEE CARDIOVASCULAR FUNCTION, BLOOD PRESSURE

PRESSURE, MECHANICAL
 SEE PHYSICAL PROPERTIES, MECHANICAL PRESSURE

PREVENTION
 SEE HEALTH, DISEASE PREVENTION AND CONTROL

PREVENTIVE DENTISTRY
 SEE DENTISTRY, PREVENTIVE

PREVENTIVE MEDICINE
 SEE HEALTH, DISEASE PREVENTION AND CONTROL

PRIMATES
 SEE MAMMALS, PRIMATES*

PROCARYOTE
 SEE BACTERIA (GENERAL)*

PROCOLLAGEN
 SEE ALBUMINOIDS, COLLAGEN, PROCOLLAGEN

PROGESTERONE ANALOGS, MEDROXYPROGESTERONE ACETATE
 R010E-04039-04 Sex steroid metabolism in oral tissues

PROGESTINS
 R010E-04039-04 Sex steroid metabolism in oral tissues
 R010E-05168-03 Glucocorticoid receptors and cleft palate (mice)

PROGNOSIS (DISEASE RELATED)
 SEE DISEASES, PROGNOSIS

PROGRAMMING, COMPUTER
 SEE COMPUTER PROGRAMMING*

PROLINE
 SEE CYCLIC AMINO ACIDS, PROLINE

PRONASE
 SEE PROTEASES AND PEPTIDASES, PRONASE

PRONENESS TO DISEASE
 SEE DISEASE PRONENESS-RISK

PROPANOLOL
 SEE NAPHTHYLAMINES, PROPRANOLOL

PROPIONIBACTERIUM
 SEE BACTERIA, PROPIONIBACTERIACEAE, PROPIONIBACTERIUM*

PROPRANOLOL
 SEE NAPHTHYLAMINES, PROPRANOLOL

PROPRIOCEPTION
 SEE SENSORY-PERCEPTUAL PROCESSES, PROPRIOCEPTION

PROSENCEPHALON
 SEE BRAIN, PROSENCEPHALON (GENERAL)

PROSTAGLANDIN SYNTHETASE
 SEE OXIDOREDUCTASES, PROSTAGLANDIN SYNTHASE

PROSTAGLANDINS
 SEE FATTY ACIDS, UNSATURATED, PROSTAGLANDINS

PROSTAGLANDINS ANALOGS
 SEE FATTY ACIDS, UNSATURATED, PROSTAGLANDINS ANALOGS

PROSTHODONTICS
 SEE ORAL-FACIAL RESTORATION, PROSTHODONTICS

PROTEASES AND PEPTIDASES
 P500E-02600-15 0032 Support for oral biology research center - Keratohyalin in keratinization of oral mucosa and skin (human, rats)
 R010E-04278-06 Human saliva-streptococcal metabolic interactions
 R010E-04518-06 Streptococcus sanguis receptors for salivary glycoproteins
 R010E-04660-06 Keratohyalin in keratinization--Oral mucosa and skin (human)
 R010E-04897-02 Functional development of salivary glands (rats)

R010E-05049-01 Saliva-complement interactions and oral mucosal defense
 R010E-05494-02 Activation of macrophages in periodontal disease
 R010E-05512-02 Role of macrophages in periodontal disease
 R230E-05793-01 Degradation of collagen in inflammation (human gingiva)

PROTEASES AND PEPTIDASES, CATHEPSINS
 P500E-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues

PROTEASES AND PEPTIDASES, COLLAGENASE
 P500E-02600-15 0014 Support for oral biology research center - Periodontal diseases (human, rats)
 ** P500E-02623-14 0027 Center for oral health research - Collagenase in the periodontium
 R010E-03408-09 Immunopathology of gingivitis and periodontitis (monkeys, human)
 R010E-03987-07 Gingival collagen metabolism in health and disease (human, rats)
 R010E-04844-04 Stress-related bone resorption--Mechanisms of action (rats)
 R010E-05049-01 Saliva-complement interactions and oral mucosal defense
 R010E-05252-01 Bidirectional effects of subgingival dental plaque
 ** R010E-05255-03 Regulation of collagenase and bone resorption (chick embryos, mice)
 R010E-05459-02 Phenotypic-Pathogenesis of gingival overgrowth (cats)
 R010E-05512-02 Role of macrophages in periodontal disease
 ** R010E-05706-01 Role of microbial collagenases in periodontal disease
 R230E-05793-01 Degradation of collagen in inflammation (human gingiva)
 ** R010E-05817-01 Gingival collagenase--Quantitation and localization (rabbits, mice, human)

PROTEASES AND PEPTIDASES, ELASTASE
 R010E-03987-07 Gingival collagen metabolism in health and disease (human, rats)

PROTEASES AND PEPTIDASES, PRONASE
 R010E-04844-04 Stress-related bone resorption--Mechanisms of action (rats)

PROTEIN BINDING
 SEE ALSO BIOLOGICAL TRANSPORT, TRANSPORT PROTEINS (SEE ALSO SPECIFICS)
 SEE ALSO CARBOHYDRATES, PROTEIN BOUND CARBOHYDRATES
 SEE ALSO ENDOCRINOLOGY, HORMONE BINDING PROTEINS
 SEE ALSO PROTEINS, CALCIUM BINDING PROTEINS
 P010E-01850-18 0075 Nutritional sources and metabolic roles of fluoride - Metabolic handling of perfluorooctanoic acid (rats)
 P500E-02623-14 0032 Center for oral health research - Interactions of salivary agglutinins and oral bacteria
 P500E-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins
 P500E-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues
 R010E-04061-07 Salivary antibodies to S mutants--Induction and effects (monkeys)
 R010E-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
 R010E-04615-04 Fluoride-cadmium interaction in dental caries (rats, human)
 R010E-04622-05 Craniofacial anomalies and protein receptors (mice, human)
 R010E-05008-03 Basis of drug induced cleft palate (rats, mice)
 ** R010E-05289-03 Fluorine ion binding by early enamel matrix proteins (rats)

PROTEIN BOUND CARBOHYDRATES
 SEE CARBOHYDRATES, PROTEIN BOUND CARBOHYDRATES

PROTEIN DEFICIENCY
 SEE NUTRITIONAL ABNORMALITIES, PROTEIN DEFICIENCY

PROTEIN DEGRADATION
 SEE PROTEOLYSIS

PROTEIN-POLYSACCHARIDE COMPLEXES
 SEE PROTEOGLYCANS

PROTEIN STRUCTURE
 SEE PROTEINS-PEPTIDES STRUCTURE

PROTEINS
 SEE ALSO ALBUMINS
 SEE ALSO BLOOD PROTEINS
 SEE ALSO GLOBULINS
 SEE ALSO GLYCOPROTEINS
 SEE ALSO LIPOPROTEINS
 SEE ALSO MUSCLE PROTEINS (AND CONTRACTILE PROTEINS)
 SEE ALSO NUCLEIC ACIDS, MRNA
 SEE ALSO NUTRITION, DIETARY CONSTITUENTS, DIETARY PROTEINS
 SEE ALSO PEPTIDES
 SEE ALSO PHOSPHOPROTEINS
 SEE ALSO PROTEOGLYCANS
 SEE ALSO PROTEOLIPIDS

P500E-02600-15 0034 Support for oral biology research center - Salivary and oral mucosal changes after cancer chemotherapy
 P500E-02670-15 0020 Institute of Dental Research - Nutrition-Disease proneness during dental development
 R010E-03856-07 Fluoride-selenium interaction in dental caries (rats)
 R010E-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
 ** R010E-05092-03 Proteins involved in dentinogenesis
 ** R010E-05436-03 Salivary proteins in bacterial aggregation/adherence
 ** R010E-05684-01 Saliva proteins--Chemistry, genetics and oral health
 R010E-05722-02 Bactericidal activity of lactoferrin on oral flora
 ** R230E-05749-01 Salivary proline-rich proteins--Localization/secretion (monkeys)
 R010E-05800-01 Formation and biochemical composition of sea mussel
 N010E-12430-00 Investigation of anticaries vaccine in primates
 N010E-12434-00 Identify cariogenic elements of food

PROTEINS, CALCIUM BINDING PROTEINS
 ** R230E-05316-03 Salivary calcium binding proteins and oral disease

PROTEINS, DIETARY
 SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY PROTEINS

PROTEINS, MEMBRANE PROTEINS
 SEE ALSO DRUGS RECEPTORS
 SEE ALSO ENDOCRINOLOGY, HORMONE RECEPTORS
 SEE ALSO NEUROTRANSMITTERS RECEPTORS
 R010E-04174-07 Variations in the surface structures of oral bacteria
 R010E-04175-07 Variations in the surface structures of oral bacteria
 R010E-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)
 R010E-05251-02 Salivary gland secretory mechanisms (rats)
 R010E-05427-01 Adherence mechanisms of oral microbes
 ** R010E-05630-01 Matrix/cell surface in neural crest cell morphogenesis (mice, chick, quail)

PROTEINS, VIRAL (GENERAL)
 ** P500E-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus

PROTEINS BIOSYNTHESIS
 SEE ALSO CELL COMPONENTS, RIBOSOMES
 SEE ALSO GENETICS, GENETIC COILING
 SEE ALSO GENETICS, GENETIC REGULATION, GENETIC INDUCTION-REPRESSION-DEREPRESSION, TRANSLATION
 SEE ALSO GLOBULINS, GAMMA GLOBULINS, IMMUNOGLOBULIN BIOSYNTHESIS
 SEE ALSO IMMUNOLOGY, ANTIBODY FORMATION
 SEE ALSO NUCLEIC ACIDS, MRNA
 ** R010E-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
 ** P500E-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)
 P500E-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus
 ** P500E-02623-14 0026 Center for oral health research - Collagen biosynthesis in the periodontium
 P500E-02668-15 0176 Regional dental research center - Collagen biochemistry and the myeloblastosis associated virus infected cells
 P500E-02668-15 0193 Regional dental research center - Metabolism of isolated ameloblasts
 P500E-02670-15 0019 Institute of Dental Research - Chemistry and molecular biology of the connective tissue protein, collagen
 P010E-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)
 R010E-03246-12 Biochemical mechanisms relevant to dentistry (bacteria)
 R010E-03469-10 Teratogens effects on cleft palate formation (mice)
 R010E-03658-17 Genetic polymorphisms of saliva (human)
 R010E-04008-07 Cellular and developmental control of calcification (tissue culture)
 R010E-04039-04 Sex steroid metabolism in oral tissues
 R010E-04224-07 Genetics of oral microflora
 R010E-04511-06 Stability of differentiation--Craniofacial study (human, hamsters)
 R010E-04622-05 Craniofacial anomalies and protein receptors (mice, human)
 R010E-04657-05 Abnormal palatal development induced by hadacidin (fungi)
 R010E-04960-03 Mechanisms of salivary gland development (mice, rats)
 R010E-05379-01 Morphogenesis and maturation of craniofacial sutures (animals)
 R010E-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)
 R010E-05636-01 Cellular mediators in tooth maintenance and repair (rats)
 R010E-05678-02 Salivary changes after cancer chemotherapeutic drugs

(contd)

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 **Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

- R23DE-05735-01 Role of hyaluronate in primary palate morphogenesis (mice embryos)
 R23DE-05749-01 Salivary proline-rich proteins—Localization/secretion (monkeys)
 R23DE-05967-01 Role of prostaglandin E in periodontal disease activity
 R01DE-05999-01 The role of nutrition in oral health
- PROTEINS DENATURATION**
 R01DE-03318-10 The molecular nature of gingival and mucosal collagen (rat)
- PROTEINS METABOLISM**
 SEE ALSO PROTEINS BIOSYNTHESIS
 SEE ALSO PROTEOLYSIS
 ** R01DE-04278-06 Human saliva-streptococcal metabolic interactions
- PROTEINS-PEPTIDES STRUCTURE**
 SEE ALSO ENZYME STRUCTURE
 ** R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
 ** P50DE-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus
 ** P50DE-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology
 ** P50DE-02670-15 0001 Institute of Dental Research - Crystal structures of calcium and phosphate complexes and of related proteins
 ** P50DE-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues
 R01DE-03301-11 Connective tissue of the periodontium—Collagen maturation
 R01DE-03318-10 The molecular nature of gingival and mucosal collagen (rat)
 ** R01DE-04125-06 Gingival matrix proteins and periodontal disease (human, mammals)
 R01DE-04645-04 A genetic-biochemical analysis of spirochete motility
 R01DE-05476-02 Novel peptide derived sweeteners
 ** R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)
 R23DE-05956-01 The adhesive of *Mytilus edulis*
- PROTEINS-PEPTIDES STRUCTURE, AMINO ACIDS SEQUENCE**
 R01DE-D1374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
 P50DE-02668-15 0152 Regional dental research center - Primary structure of proteins in hemostasis and oral biology
 P50DE-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues
 P50DE-02670-15 0024 Institute of Dental Research - Metabolism of connective tissue proteoglycans
 ** R01DE-03658-17 Genetic polymorphisms of saliva (human)
 R01DE-03731-06 Dextran sucrose of *Streptococcus sanguis*
 R01DE-05467-02 Pathogenesis of localized bone destruction
 R23DE-05749-01 Salivary proline-rich proteins—Localization/secretion (monkeys)
- PROTEINS STRUCTURE**
 SEE PROTEINS-PEPTIDES STRUCTURE
- PROTEINS TRANSPORT**
 SEE ALSO PROTEIN BINDING
 R01DE-04897-02 Functional development of salivary glands (rats)
- PROTEOGLYCANS**
 SEE ALSO GLYCOPROTEINS
 SEE ALSO METALLOPROTEINS, TRANSFERRIN
 SEE ALSO PEPTIDOGLYCANS
 ** P50DE-02670-15 0024 Institute of Dental Research - Metabolism of connective tissue proteoglycans
 ** P50DE-02670-15 0029 Institute of Dental Research - Structure of connective tissue proteoglycans (cattle)
 ** P50DE-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues
 P50DE-02731-15 0032 Development support for dental research institute - Epithelial cell basal lamina biosynthesis (rats)
 R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)
 R01DE-04141-07 Mechanism of hard tissue mineralization (human, rats)
 R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)
 R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine
 R01DE-05379-01 Morphogenesis and maturation of craniofacial sutures (animals)
 R01DE-05483-02 Characterization of predental extracellular fluid (rats)
- PROTEOGLYCANS, MUCIN**
 P01DE-D2847-13 0020 Microbial ecology and its relation to dental disease - Acquisition transmission and localization of human oral bacteria
 R01DE-04518-06 *Streptococcus sanguis* receptors for salivary glycoproteins
 R01DE-04971-03 Human salivary antigens—Characterization (monkeys)

R23DE-05777-01 Cationic protein in submandibular saliva (goats, rabbits, human)

PROTEOLIPIDS

- SEE ALSO LIPOPROTEINS
 R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues
 ** R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

PROTEOLYSIS

- P50DE-02600-15 0003 Support for oral biology research center - Disorders of connective tissue metabolism (human)
 P50DE-02668-15 0190 Regional dental research center - Thrombin and prothrombin
 ** R01DE-04278-06 Human saliva-streptococcal metabolic interactions
 R01DE-05722-02 Bactericidal activity of lactoferrin on oral flora
 ** R23DE-05793-01 Degradation of collagen in inflammation (human gingiva)

PROTEOLYTIC ENZYMES

SEE PROTEASES AND PEPTIDASES

PROTHROMBIN

SEE BLOOD COAGULATION, PROTHROMBIN

PROWER FACTOR

SEE BLOOD COAGULATION, FACTOR X

PSYCHIC ACTIVITY LEVEL, AROUSAL

- R23DE-05527-02 Behavioral treatments for nocturnal bruxism (human)

PSYCHIC ACTIVITY LEVEL, RELAXATION

- R01DE-04494-05 Control of stress during dental procedures (human)
 R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)

PSYCHIC ACTIVITY LEVEL, SLEEP

- ** R23DE-05036-03 Nocturnal masseter muscle activity and jaw dysfunction (human)

PSYCHOACOUSTICS

SEE PSYCHOPHYSICS, PSYCHOACOUSTICS

PSYCHOBIOLOGY, PSYCHOPHYSIOLOGY

SEE ALSO BEHAVIORAL MEDICINE
 SEE ALSO BIO-PSYCHOLOGY STUDY SECTION
 SEE ALSO INFORMATION PROCESSING AND CONTROL (NEURAL)
 SEE ALSO PSYCHOLOGIC STRESS
 SEE ALSO PSYCHOMOTOR FUNCTION
 SEE ALSO PSYCHOPHYSIOLOGIC DISORDERS
 SEE ALSO SENSORY-PERCEPTUAL PROCESSES, SENSORY MECHANISMS (GENERAL)

- ** P50DE-02668-15 0210 Regional dental research center - Somesthetic capacities of human subjects (monkeys)
 R01DE-04004-07 Acupuncture and perception of dental pain (human)
 R01DE-04494-05 Control of stress during dental procedures (human)

PSYCHOLOGIC STRESS

- SEE ALSO PSYCHOPHYSIOLOGIC DISORDERS
 R01DE-04358-06 Treatment of temporomandibular joint pain
 ** R01DE-04494-05 Control of stress during dental procedures (human)
 R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)
 R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)
 R01DE-05369-03 Factors affecting dental postoperative pain

PSYCHOLOGICAL ADAPTATION, COPING BEHAVIOR

- R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)
 R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)
 ** R23DE-05858-01 Dentists' behavior and treatment outcomes

PSYCHOLOGICAL ADAPTATION, EMOTIONAL ADJUSTMENT

- SEE ALSO PSYCHOLOGY SOCIAL, SOCIAL ADJUSTMENT
 R01DE-04779-04 Behavioral stages for cleft palate patients
 R01DE-05371-01 Psychosocial evaluation of craniofacial patients

PSYCHOLOGICAL IMPACT OF DISEASES OR MEDICAL PROCEDURES

SEE BEHAVIORAL MEDICINE

PSYCHOLOGY, ATTITUDE TO HEALTH AND HEALTH PROBLEMS

- R01DE-04358-06 Treatment of temporomandibular joint pain
 R01DE-04494-05 Control of stress during dental procedures (human)

PSYCHOLOGY, ATTITUDES (AND RELATED)

- SEE ALSO THERAPY COMPLIANCE
 R01DE-D5511-02 Evanston-Oak park fluoridation study after 25 years (human)

PSYCHOLOGY, ATTITUDES, PERSONAL SATISFACTION

- R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)

PSYCHOLOGY, BEHAVIOR

SEE ALSO CHILD MENTAL DEVELOPMENT, CHILD BEHAVIOR
 SEE ALSO INFORMATION-COMMUNICATION BEHAVIOR
 SEE ALSO PSYCHOLOGICAL ADAPTATION, COPING BEHAVIOR
 SEE ALSO PSYCHOLOGY, PERSONALITY
 SEE ALSO PSYCHOLOGY SOCIAL, INTERPERSONAL RELATIONS
 SEE ALSO THERAPY COMPLIANCE
 P01DE-05130-03 0006 Dental/orofacial pain—Mechanisms behavior and modulation - Acute pain in research and clinical settings

PSYCHOLOGY, BEHAVIOR ANIMAL

- P50DE-02668-15 0209 Regional dental research center - Static and dynamic properties of S-I neurons in the behaving macaque monkey
 R01DE-05208-03 Mechanism of dental and facial sensation (monkeys)

PSYCHOLOGY, COGNITION

SEE ALSO SENSORY-PERCEPTUAL PROCESSES, PERCEPTION
 P01DE-05130-03 0006 Dental/orofacial pain—Mechanisms behavior and modulation - Acute pain in research and clinical settings

PSYCHOLOGY, COGNITION, EXPECTANCY

- R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)

PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL CONTROL

- ** R01DE-04358-06 Treatment of temporomandibular joint pain
 R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)
 ** R01DE-05204-03 Operant neural control in trigeminal pain systems (rat)

PSYCHOLOGY, CONDITIONING, OPERANT

- ** R01DE-05204-03 Operant neural control in trigeminal pain systems (rat)

PSYCHOLOGY, CONDITIONING, REINFORCEMENT

- R23DE-05799-01 Behavioral methods for pedodontic management (human)

PSYCHOLOGY, EMOTIONS, ANXIETY

SEE ALSO DENTAL FEAR AND ANXIETY
 R01DE-04494-05 Control of stress during dental procedures (human)

PSYCHOLOGY, EMOTIONS, PLEASURE-DISPLEASURE (GENERAL)

- R01DE-04494-05 Control of stress during dental procedures (human)

PSYCHOLOGY, HABITS, SMOKING

- R01DE-05330-02 Herpes virus antibodies in patients with oral cancer

PSYCHOLOGY, LEARNING, REHEARSAL

- R23DE-05527-02 Behavioral treatments for nocturnal bruxism (human)

PSYCHOLOGY, MOTIVATION

- R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)

PSYCHOLOGY, PERSONALITY

SEE ALSO PSYCHOLOGY, ATTITUDES (AND RELATED)
 SEE ALSO PSYCHOLOGY, BEHAVIOR
 R01DE-04358-06 Treatment of temporomandibular joint pain
 R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)

PSYCHOLOGY, PERSONALITY DEVELOPMENT, PSYCHOSEXUAL DEVELOPMENT

- R01DE-04779-04 Behavioral stages for cleft palate patients

PSYCHOLOGY, PERSONALITY DEVELOPMENT, SELF-CONCEPT

- R01DE-04779-04 Behavioral stages for cleft palate patients
 R01DE-05371-01 Psychosocial evaluation of craniofacial patients
 R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)

PSYCHOLOGY ABNORMAL, NEUROSIS

- R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)

PSYCHOLOGY DEVELOPMENTAL (CHILD MENTAL DEVELOPMENT)

SEE CHILD MENTAL DEVELOPMENT

PSYCHOLOGY SOCIAL (SEE ALSO SOCIAL...)

- SEE ALSO FAMILY
 R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate
 ** R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)

PSYCHOLOGY SOCIAL, COOPERATION

- R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
 **Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

PSYCHOLOGY SOCIAL, GROUP PROCESSES, PEER GROUPS

- R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)

PSYCHOLOGY SOCIAL, GROUP PROCESSES, ROLE

- R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)

PSYCHOLOGY SOCIAL, INTERPERSONAL RELATIONS

- SEE ALSO HEALTH CARE SERVICES, PATIENT-PROFESSIONAL RELATIONS

PSYCHOLOGY SOCIAL, SOCIAL ADJUSTMENT

- SEE ALSO PSYCHOLOGICAL ADAPTATION, EMOTIONAL ADJUSTMENT

PSYCHOLOGY SOCIAL, SOCIAL ADJUSTMENT

- R01DE-04779-04 Behavioral stages for cleft palate patients
R01DE-05371-01 Psychosocial evaluation of craniofacial patients

PSYCHOMOTOR DISORDERS

- R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

PSYCHOMOTOR FUNCTION

- R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

PSYCHOPHARMACOLOGICAL AGENTS, HYPNOTICS AND SEDATIVES

- P01DE-05130-03 0006 Dental/orofacial pain—Mechanisms behavior and modulation - Acute pain in research and clinical settings

PSYCHOPHYSICS

- R01DE-04004-07 Acupuncture and perception of dental pain (human)
R01DE-05208-03 Mechanism of dental and facial sensation (monkeys)

PSYCHOPHYSICS, PSYCHOACOUSTICS

- R01DE-05203-03 Speech adaptations to orthognathic surgery (human)

PSYCHOPHYSIOLOGIC DISORDERS

- SEE ALSO BEHAVIORAL MEDICINE
SEE ALSO PSYCHOLOGICAL STRESS
R01DE-05679-01 Pathophysiology of MPD and other facial pain syndromes (animals)

PSYCHOPHYSIOLOGY

- SEE PSYCHOBIOLOGY, PSYCHOPHYSIOLOGY

PSYCHOSEXUAL DEVELOPMENT

- SEE PSYCHOLOGY, PERSONALITY DEVELOPMENT, PSYCHOSEXUAL DEVELOPMENT

PSYCHOSOMATIC DISORDERS

- SEE PSYCHOPHYSIOLOGIC DISORDERS

PSYCHOTHERAPY, BEHAVIOR MODIFICATION

- SEE ALSO PSYCHOTHERAPY, DESENSITIZATION
R01DE-04494-05 Control of stress during dental procedures (human)
R01DE-05305-02 Behavioral approaches to pain responses in pedodontics (children)
R23DE-05527-02 Behavioral treatments for nocturnal bruxism (human)

PSYCHOTHERAPY, DESENSITIZATION

- R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)

PT

- SEE METALS, HEAVY METALS, PLATINUM (COMPOUNDS)

PTFE

- SEE PLASTICS, FLUOROCARBON POLYMERS

PUBERTY

- SEE CHILD DEVELOPMENT, PUBERTY

PUBLICATIONS

- R01DE-05904-01 Revision of the F.O.I dental lexicon

PUERILE

- SEE CHILDREN

PULP

- SEE DENTAL STRUCTURE, PULP

PULP DISORDERS, DENTAL

- SEE DENTAL PULP DISORDERS

PULP FLUID

- SEE DENTAL STRUCTURE, PULP FLUID

PULPOTOMY

- SEE DENTISTRY, ENDODONTICS, PULPOTOMY

PURE LINES

- SEE GENETICS, POPULATION GENETICS, INBREEDING

PURINE NUCLEOSIDES, ADENINE NUCLEOSIDES, ADENINE ARABINOSIDE

- R23DE-05572-02 NEW antiviral therapy for oral and other herpes (mice, guinea pig, rabbits)

PURINE NUCLEOTIDES

- R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)

PURINE NUCLEOTIDES, ADENINE NUCLEOTIDES, AMP CYCLIC

- R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)
R01DE-03666-07 X-ray therapeutic index for salivary glands
R01DE-03715-06 Cellular assembly—Its role in facial morphogenesis (fungi)
R01DE-04008-07 Cellular and developmental control of calcification (tissue culture)
R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism
R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)
P50DE-05139-04 0003 Clinical research center for periodontal disease
R01DE-05251-02 Salivary gland secretory mechanisms (rats)
R01DE-05322-01 Genetic analysis of birth defects involving septa (human, mice)
R23DE-05393-03 Factors association with hyperplasia of oral mucosa
R01DE-05412-02 Electric current, bone remodeling and tooth movement (cats)
R01DE-05413-02 Bone resorption in periodontal disease
R01DE-05550-01 Cell death during craniofacial embryogenesis
R23DE-05592-02 Biochemical mechanism of steroid-induced clefting (mice)
R01DE-05632-01 Development of salivary gland secretory function (rats)
R01DE-05764-02 Cellular pharmacology of salivary secretion (rats)

PURINE NUCLEOTIDES, ADENINE NUCLEOTIDES, ATP

- P50DE-02623-14 0030 Center for oral health research - Role of mitochondria in the mineralization process (chickens)

PURINE NUCLEOTIDES, GUANINE NUCLEOTIDES, GMP CYCLIC

- R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)
R01DE-05249-02 Salivary secretion—role of calcium (mice)
R01DE-05412-02 Electric current, bone remodeling and tooth movement (cats)
R01DE-05550-01 Cell death during craniofacial embryogenesis

PURINES, XANTHINES, THEOPHYLLINE

- R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)

PYRANOSSES

- SEE CARBOHYDRATES, PYRANOSSES

PYRIDINE NUCLEOTIDES

- R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism

PYRIDINE NUCLEOTIDES, NICOTINAMIDE RIBOTIDES, NADP(H2)

- R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)

PYRIDOXAL ANALOGS

- SEE VITAMIN B6, PYRIDOXAL ANALOGS

PYRIMIDINE NUCLEOSIDES, THYMINE NUCLEOSIDES, THYMIDINE

- R01DE-06000-01 Effect of parotid function on saliva and cells

PYRIMIDINE NUCLEOTIDES

- R01DE-05089-03 Oral herpes simplex—An approach to dental therapy (hamsters)

PYRIMIDINES, BARBITURATES, PHENOBARBITAL

- R01DE-04039-04 Sex steroid metabolism in oral tissues

PYRUVATE KINASE

- SEE PHOSPHOTRANSFERASES, ATP:PYRUVATE PHOSPHOTRANSFERASE

PYRUVATES

- SEE FATTY ACIDS, PYRUVATES

QA.2 ANTIGENS

- SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

QUADRUPLTS

- SEE FAMILY, TWINS AND MULTIPLETS

QUALITY OF FOODS

- SEE FOOD SCIENCES AND TECHNOLOGY, FOOD QUALITY-STANDARDS

QUALITY OF HEALTH CARE

- SEE HEALTH CARE QUALITY

QUATERNARY AMMONIUM COMPOUNDS

- SEE AMMONIUM QUATERNARY

QUESTIONNAIRES

- SEE INFORMATION GATHERING (DATA COLLECTION), QUESTIONNAIRES

QUINTUPLETS

- SEE FAMILY, TWINS AND MULTIPLETS

RACIAL STOCKS

- SEE SOCIAL GROUPS, RACIAL STOCKS

RADIATION, ELECTROMAGNETIC WAVES, ULTRAVIOLET RAYS (290NM TO 380NM)

- P50DE-02668-15 0150 Regional dental research center - Polymerization of tooth restorative composite materials

RADIATION, ELECTROMAGNETIC WAVES, X-RAYS

- R01DE-03666-07 X-ray therapeutic index for salivary glands
R01DE-03996-06 Low level irradiation-modification of carcinogenesis
R01DE-04783-04 The development of a dental x-ray aiming device
R01DE-05868-01 Multivariate analysis of craniofacial growth in clefting

RADIATION, IONIZING RADIATION

- R01DE-04783-04 The development of a dental x-ray aiming device

RADIATION ASSOCIATED CARCINOGENESIS

- SEE NEOPLASTIC TRANSFORMATION, CARCINOGENESIS, RADIATION

RADIATION DOSAGE AND DOSIMETRY

- R01DE-03666-07 X-ray therapeutic index for salivary glands
R01DE-03996-06 Low level irradiation-modification of carcinogenesis

RADIATION EFFECTS

- SEE ALSO NEOPLASMS, RADIATION INDUCED
SEE ALSO NEOPLASTIC TRANSFORMATION, CARCINOGENESIS, RADIATION
SEE ALSO RADIATION SENSITIVITY
R01DE-03666-07 X-ray therapeutic index for salivary glands

RADIATION INDUCED NEOPLASMS

- SEE NEOPLASMS, RADIATION INDUCED

RADIATION PROTECTION DRUGS

- SEE RADIOLOGICAL HEALTH, RADIATION PROTECTION DRUGS

RADIATION SENSITIVITY

- R01DE-03666-07 X-ray therapeutic index for salivary glands

RADIATION SENSITIVITY, RADIOSENSITIZERS

- R01DE-03666-07 X-ray therapeutic index for salivary glands

RADIATION SENSITIZING AGENTS

- SEE RADIATION SENSITIVITY, RADIOSENSITIZERS

RADIATION STUDY SECTION

- R01DE-03666-07 X-ray therapeutic index for salivary glands
R01DE-03996-06 Low level irradiation-modification of carcinogenesis
R01DE-04783-04 The development of a dental x-ray aiming device

RADIOASSAY (RADIOMETRY)

- SEE ALSO RADIOAUTOGRAPHY*
SEE ALSO RADIOGRAPHY*
SEE ALSO RADIOIOTRACERS*
R01DE-03180-11 Microbiologic studies of the human oral streptococci

RADIOAUTOGRAPHY*

- P50DE-02670-15 0035 Institute of Dental Research - Granulocyte growth and division

RADIOBIOLOGY (GENERAL)

- SEE RADIATION EFFECTS

RADIO DIAGNOSIS AND RADIO DIAGNOSTIC METHODS

- R01DE-04783-04 The development of a dental x-ray aiming device

RADIO DIAGNOSTIC METHODS

- SEE RADIO DIAGNOSIS AND RADIO DIAGNOSTIC METHODS

RADIOGRAPHY*

- SEE ALSO BRAIN VISUALIZATION, ENCEPHALOGRAPHY*
SEE ALSO DENTAL VISUALIZATION, DENTAL RADIOGRAPHY*
SEE ALSO RADIOAUTOGRAPHY*
R01DE-02872-12 0034 Craniofacial dysmorphology - Digitization of roentgencephalometric data (human)
P01DE-02872-12 0058 Craniofacial dysmorphology - Ophthalmology (human, rabbits)
P01DE-02872-12 0063 Craniofacial dysmorphology - Premature craniofacial synostoses (human)

RADIOGRAPHY, SCANNING, DSR

- R01DE-03703-05 Integrated three-dimensional craniofacial measurement (human)

RADIOIMMUNOASSAY

- SEE IMMUNOLOGICAL TESTS AND IMMUNOASSAY, RADIOIMMUNOASSAY*

RADIOISOTOPE TRACERS

- SEE RADIOIOTRACERS*

RADIOLOGICAL HEALTH, RADIATION PROTECTION DRUGS

- R01DE-03666-07 X-ray therapeutic index for salivary glands

RADIOIMETRY

- SEE RADIOASSAY (RADIOMETRY)

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

RADIOSENSITIVITY

SEE RADIATION SENSITIVITY

RADIOSENSITIZERS (RADIOSENSITIZING AGENTS)

SEE RADIATION SENSITIVITY, RADIOSENSITIZERS

RADIOTRACERS*

SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, RADIOIMMUNOASSAY*

R01DE-03666-07 X-ray therapeutic index for salivary glands

RAPHE NUCLEUS, DORSAL

SEE BRAIN, MESENCEPHALON, RAPHE NUCLEUS, DORSAL

RATE OF ADMINISTRATION, DRUGS

SEE DOSAGE AND ROUTE, RATE AND DURATION OF ADMINISTRATION

RATS (LABORATORY)

SEE MAMMALS, RODENTS, MYOMORPHA, RATS (LABORATORY)*

REACTION DYNAMICS, KINETICS,**MECHANISMS**

SEE CHEMICAL REACTIONS (DYNAMICS)

RECEPTOR SITES, ENZYMES

SEE ENZYME STRUCTURE

RECEPTORS OF SENSORY STIMULI

SEE NERVOUS SYSTEM, AFFERENT NERVES

RECOMBINANT DNA, ARTIFICIALLY INDUCED

SEE GENETIC MANIPULATION

RECOMBINATION

SEE GENETICS, RECOMBINATION

REDOX

SEE OXIDATION-REDUCTION

REGENERATION

SEE GROWTH AND DEVELOPMENT, REGENERATION

REGENERATION, BONE

SEE SKELETAL SYSTEM REGENERATION, BONE REGENERATION

REGENERATION, NERVOUS SYSTEM

SEE NERVOUS SYSTEM REGENERATION

REGENERATION, SKELETAL

SEE SKELETAL SYSTEM REGENERATION

REGISTRIES, CELL CULTURE

SEE TISSUE (CELL) CULTURE, CELL CULTURE COLLECTIONS BANKS AND REGISTRIES

REGISTRIES, DISEASE (CLINICAL DISEASE)

SEE HEALTH RECORD SYSTEMS, PATIENT (DISEASE) REGISTRIES

REGISTRIES, INFORMATION

SEE INFORMATION SYSTEMS (INCL BANKS AND CENTERS)

REGISTRIES, PATIENT (OR CLINICAL DISEASE)

SEE HEALTH RECORD SYSTEMS, PATIENT (DISEASE) REGISTRIES

REGULATION (SELF) OF (VISCERAL)**RESPONSES**

SEE PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL CONTROL

REHEARSAL LEARNING

SEE PSYCHOLOGY, LEARNING, REHEARSAL

REINFORCEMENT (CONDITIONING)

SEE PSYCHOLOGY, CONDITIONING, REINFORCEMENT

RELAXATION, MUSCLE

SEE MUSCLE FUNCTION, MUSCLE RELAXATION

RELAXATION, PSYCHIC

SEE PSYCHIC ACTIVITY LEVEL, RELAXATION

RENAL HYPOPHOSPHATEMIA

SEE METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN

RENAL OSTEODYSTROPHY

SEE KIDNEY DISORDERS, RENAL RICKETS

RENAL RICKETS

SEE KIDNEY DISORDERS, RENAL RICKETS

RENAL TUBULAR TRANSPORT

SEE KIDNEY FUNCTION, RENAL TUBULAR TRANSPORT

REPLICATION, VIRAL

SEE VIRUS DEVELOPMENT, REPLICATION

REPRODUCTION MICROORGANISMS

SEE ALSO GROWTH MICROORGANISMS

SEE ALSO VIRUS DEVELOPMENT, REPLICATION

N01DE-72409-08 Effect of strontium, lithium and fluorine on dental plaque (rats, human)

REPRODUCTIVE HORMONES,**GONADOTROPINS**

R01DE-04039-04 Sex steroid metabolism in oral tissues

REPRODUCTIVE HORMONES, SEX HORMONES

SEE ALSO ANDROSTANE SERIES, ANDROGENS

SEE ALSO ESTRADIENE SERIES, ESTROGENS

SEE ALSO PROGESTINS

** R01DE-04039-04 Sex steroid metabolism in oral tissues

REPRODUCTIVE SYSTEM FEMALE, MAMMARY GLANDS, LACTATION

** P50DE-02668-15 0088 Regional dental research center -

Hypervitaminosis D in lactation

P50DE-02668-15 0192 Regional dental research center -

Skeletal actions of calcitonin in the rat

REPRODUCTIVE SYSTEM FEMALE, OVARY

R01DE-04511-06 Stability of differentiation--Craniofacial study (human, hamsters)

REPRODUCTIVE SYSTEM DISORDERS FEMALE, VAGINAL DISORDERS

P01DE-02872-12 0053 Craniofacial dysmorphology -

Maxillofacial prosthetics (human)

RESEARCH BIOMEDICAL

SEE HEALTH SCIENCES RESEARCH (GENERAL)*

RESEARCH FACILITIES

SEE BIOMEDICAL FACILITIES

SEE CLINICAL RESEARCH CENTERS

SEE GENERAL MEDICINE STUDY SECTION

RESINS

SEE MOLECULAR CONDENSATIONS, RESINS

RESORPTION OF BONE, ABNORMAL

SEE SKELETAL DISORDERS, BONE RESORPTION ABNORMAL

RESORPTION OF BONE, NORMAL

SEE SKELETAL SYSTEM, BONE RESORPTION-REMODELING PHYSIOLOGIC

RESORPTION OF TEETH

SEE DENTAL DISORDERS, TOOTH RESORPTION

RESPIRATION

SEE RESPIRATORY FUNCTION, RESPIRATION

RESPIRATION INTERNAL

SEE ALSO OXIDOREDUCTASES

R01DE-02212-13 Circulation in teeth and supporting

structures (dogs, monkeys)

** P50DE-02668-15 0193 Regional dental research center -

Metabolism of isolated ameloblasts

RESPIRATORY AIRFLOW DISORDERS

SEE RESPIRATORY DISORDERS, RESPIRATORY AIRFLOW DISORDERS

RESPIRATORY ANESTHESIA (INHALATION ANESTHESIA)

SEE SENSORY DEPRESSION, ANESTHESIA (GENERAL), INHALATION

RESPIRATORY DISORDERS, RESPIRATORY AIRFLOW DISORDERS

SEE ALSO HYPERSENSITIVITY, RESPIRATORY HYPERSENSITIVITY, ASTHMA

** R23DE-05942-01 Airway factors in cleft palate dentofacial deformity

RESPIRATORY FUNCTION

SEE ALSO INFORMATION-COMMUNICATION BEHAVIOR, SPEECH

R01DE-05558-01 Sensory alterations of craniofacial form (Rhesus monkeys)

RESPIRATORY FUNCTION, RESPIRATION

P01DE-02872-12 0038 Craniofacial dysmorphology -

Evaluation of craniofacial surgery

P01DE-05130-03 0006 Dental/orofacial pain--Mechanisms

behavior and modulation - Acute pain in research and clinical settings

RESPIRATORY GAS CONSUMPTION, OXYGEN CONSUMPTION

R01DE-03993-07 Effect of saliva on the metabolism of dental plaque

RESPIRATORY GAS LEVELS, OXYGEN TENSION

P50DE-02623-14 0030 Center for oral health research - Role

of mitochondria in the mineralization process (chickens)

R01DE-05495-02 Myofibroblast contraction in periodontium

(rats)

RESPIRATORY GASES, CARBON DIOXIDE

R01DE-05354-04 Prevention of dental caries (rats, human)

RESPIRATORY GASES, OXYGEN

R01DE-01912-18 Tooth enamel apatite at the atomic level (human)

RESPIRATORY INFECTIONS

P50DE-02600-15 0039 Support for oral biology research center - Saliva in abnormal bacterial adherence and

colonization (human)

RESPIRATORY SYSTEM, LARYNX

R01DE-03631-08 Physiological study of speech adaptation (human)

RESPIRATORY SYSTEM, LARYNX, EPIGLOTTIS

** R01DE-05728-01 Role of chemoreceptors in craniofacial function (lambs)

RESPIRATORY SYSTEM, LUNG ALVEOLUS

R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

RESPONSE

SEE STIMULUS-RESPONSE (GENERAL)

RETICULAR DYSGENESIS

SEE IMMUNOPATHOLOGY, IMMUNOLOGIC DEFICIENCY DISORDERS

RETINOIC ACID

SEE VITAMIN A ANALOGS

RETINOL

SEE VITAMIN A ANALOGS

RETINOL

SEE VITAMIN A

RETINYL ACETATE

SEE VITAMIN A ANALOGS

RETRIEVAL, INFORMATION

SEE INFORMATION SYSTEMS, INFORMATION RETRIEVAL

RETROVIRIDAE

SEE VIRUSES, RETROVIRIDAE

RETROVIRUSES (C-TYPE RNA VIRUSES)

SEE VIRUSES, RETROVIRIDAE

REVASCULARIZATION SURGICAL

SEE CARDIOVASCULAR SURGERY, REVASCULARIZATION SURGICAL

RHEOLOGY AIR

SEE RESPIRATORY DISORDERS, RESPIRATORY AIRFLOW DISORDERS

RHEOLOGY LIQUIDS

SEE CARDIOVASCULAR FUNCTION, BLOOD FLOW

SEE PHYSICAL PROPERTIES, FLUID FLOW

RHEUMATOID ARTHRITIS

SEE SKELETAL DISORDERS, ARTHRITIS, RHEUMATOID

RHL-A LOCUS (RHESUS MONKEY)

SEE IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)

RI-1 LOCUS

SEE IMMUNOGENETICS, IMMUNOGLOBULIN GENES AND CONTROL

RIBONUCLEASE

SEE NUCLEASES, RIBONUCLEASE

RIBONUCLEIC ACID(S)

SEE NUCLEIC ACIDS, RNA

RIBONUCLEIC ACIDS REPLICATION

SEE NUCLEIC ACIDS SYNTHESIS, RNA

RIBONUCLEOSIDES MONO-, DI-,**TRIPHOSPHATES**

SEE NUCLEOTIDES, RIBONUCLEOTIDES

RIBONUCLEOSIDES PHOSPHATES

SEE NUCLEOTIDES, RIBONUCLEOTIDES

RIBONUCLEOTIDES

SEE NUCLEOTIDES, RIBONUCLEOTIDES

RIBOSOMES

SEE CELL COMPONENTS, RIBOSOMES

RICKETS, RENAL

SEE KIDNEY DISORDERS, RENAL RICKETS

RICKETS, VITAMIN D RESISTANT

SEE METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN

RISK, DISEASE PRONENESS

SEE DISEASE PRONENESS-RISK

RL-A LOCUS (RABBIT)

SEE IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)

RNA

SEE NUCLEIC ACIDS, RNA

RNA BIOSYNTHESIS

SEE NUCLEIC ACIDS SYNTHESIS, RNA

RNA CLONING

SEE NUCLEIC ACIDS CLONING

RNA REPLICATION

SEE NUCLEIC ACIDS SYNTHESIS, RNA

RODS, GRAM-NEGATIVE

SEE BACTERIA, GRAM-NEGATIVE*

RODS, GRAM-POSITIVE

SEE BACTERIA, GRAM-POSITIVE*

ROLE

SEE PSYCHOLOGY SOCIAL, GROUP PROCESSES, ROLE

ROOT CANAL FILLING MATERIALS

SEE DENTAL MATERIALS, ROOT CANAL FILLING MATERIALS

ROOT CANAL THERAPY

SEE DENTISTRY, ENDODONTICS, ROOT CANAL THERAPY

ROTHIA DENTOCARIOSIA

SEE BACTERIA, ACTINOMYCETALES, ROTHIA DENTOCARIOSIA

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

(contd.)

ROUTE OF ADMINISTRATION

SEE DOSAGE AND ROUTE, ROUTE OF ADMINISTRATION

RURAL AREAS

SEE SOCIOENVIRONMENT, RURAL AREAS

S REGION GENES

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

SACCHARIN

SEE FOOD, SWEETENING AGENTS

SAFETY EQUIPMENT-ENGINEERING

SEE INJURY (HAZARDS) PREVENTION AND CONTROL, SAFETY EQUIPMENT-ENGINEERING

SAFETY OF MEDICAL EQUIPMENT

SEE BIOMEDICAL ENGINEERING, MEDICAL EQUIPMENT SAFETY

SALICYLAMIDE

SEE PHENYLAMIDES, SALICYLAMIDE

SALICYLATES

SEE PHENYLCARBOXYLATES, SALICYLATES

SALIVA

SEE ORAL-PHARYNGEAL, SALIVA

SALIVARY GLANDS

SEE ORAL-PHARYNGEAL, SALIVARY GLANDS

SALIVARY GLAND DISORDERS

SEE ORAL-PHARYNGEAL DISORDERS, SALIVARY GLAND DISORDERS

SALIVARY GLAND NEOPLASMS

SEE NEOPLASMS OF ORAL-PHARYNGEAL STRUCTURES, SALIVARY GLAND NEOPLASMS

SALIVATION

SEE ORAL-PHARYNGEAL, SALIVATION

SALMONELLA INFECTIONS

SEE BACTERIAL DISEASES, ENTEROBACTERACEAE, SALMONELLA INFECTIONS

SALMONELLA-MICROSOME TEST FOR MUTAGENS

SEE GENETICS, MUTAGENS, MUTAGEN TESTS

SALTS

SEE CHEMICALS (GENERAL), SALTS (GENERAL)

SALTS, DIETARY

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY SALTS

SARCOMERES

SEE MUSCLE CELLS, SARCOMERES

SATISFACTION

SEE PSYCHOLOGY, ATTITUDES, PERSONAL SATISFACTION

SCALLOPS

SEE MOLLUSKS, PELECYPODS*

SCANDINAVIAN COUNTRIES

SEE GEOGRAPHICAL SITES, EUROPE, SCANDINAVIAN COUNTRIES

SCANNING ELECTRON MICROSCOPY

SEE OPTICS, MICROSCOPY, ELECTRON SCANNING*

SCANNING-PRODUCED MOTION IMAGES

SEE RADIOGRAPHY, SCANNING, DSR

SCARS

SEE INJURIES, SCARS

SCHEDULE, DOSAGE

SEE DOSAGE AND ROUTE, DOSAGE

SCHIFF BASES

SEE IMINES, SCHIFF BASES

SCHOOLS

SEE EDUCATION, SCHOOLS

SCLEDERMA

SEE CONNECTIVE TISSUE DISORDERS, SCLERODERMA

SCLEROSIS PROGRESSIVE SYSTEMIC

SEE CONNECTIVE TISSUE DISORDERS, SCLERODERMA

SCREENING

SEE DRUGS SCREENING

SE

SEE METALS, METALLOIDS, SELENIUM (COMPOUNDS)

SEAFOOD

SEE FOOD, SEAFOOD

SEALANTS, DENTAL

SEE DENTAL MATERIALS, DENTAL ADHESIVES AND SEALANTS

SEALASE

SEE NUCLEIC ACIDS REPAIR, DNA REPAIR (ENZYME)

SECONDARY DISEASE (TRANSPLANTATION)

SEE TISSUE COMPATIBILITY-TRANSPLANT, GRAFT VERSUS HOST REACTIONS

SECRETION OF CELL WASTES

SEE BIOLOGICAL TRANSPORT, SECRETORY MECHANISMS, EXCRETION

SECRETORY IMMUNOGLOBULIN A

SEE IMMUNOLOGY, SECRETORY (ANTIBODY) (FACTOR) SYSTEM

SECRETORY MECHANISMS

SEE BIOLOGICAL TRANSPORT, SECRETORY MECHANISMS

SECRETORY (ANTIBODY) (FACTOR) SYSTEM

SEE IMMUNOLOGY, SECRETORY (ANTIBODY) (FACTOR) SYSTEM

SEDATIVES

SEE PSYCHOPHARMACOLOGICAL AGENTS, HYPNOTICS AND SEDATIVES

SELENIUM (COMPOUNDS)

SEE METALS, METALLOIDS, SELENIUM (COMPOUNDS)

SELF-CONCEPT

SEE PSYCHOLOGY, PERSONALITY DEVELOPMENT, SELF-CONCEPT

SELF REGULATION (CONTROL) OF AUTONOMIC (VISCERAL) RESPONSES

SEE PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL CONTROL

SENIOR CITIZENS

SEE AGE (HUMAN), ADULT, OLD AGE (65 TO 99 YRS)

SENSE ORGANS, CHEMORECEPTORS

SEE ALSO SENSORY-PERCEPTUAL PROCESSES, TASTE

** R01DE-05728-01 Role of chemoreceptors in craniofacial function (lambs)

SENSORIMOTOR SYSTEMS (GENERAL)

SEE NEUROMOTOR SYSTEM, SENSORIMOTOR SYSTEMS (GENERAL)

SENSORY DEPRESSION, ANALGESIA

SEE ALSO NEUROPHARMACOLOGICAL AGENTS, ANALGESICS

** R01DE-05204-03 Operant neural control in trigeminal pain systems (rat)
R01DE-05369-03 Factors affecting dental postoperative pain
R01DE-05390-03 Opiate action on CNS terminals of tooth pulp fibers (animals)**SENSORY DEPRESSION, ANALGESIA BY MASKING, ELECTROANALGESIA**

** R01DE-04004-07 Acupuncture and perception of dental pain (human)

SENSORY DEPRESSION, ANESTHESIA (GENERAL), INHALATION

** R23DE-05507-02 Psychomotor impairment related to N2O exposure (human)

SENSORY DEPRESSION, ANESTHESIA DENTAL

** R01DE-04004-07 Acupuncture and perception of dental pain (human)

SENSORY DISORDERS

SEE SENSORY-PERCEPTUAL DISORDERS, SENSORY DISORDERS

SENSORY FEEDBACK

SEE ALSO EYE, VISUAL FEEDBACK

R01DE-04358-06 Treatment of temporomandibular joint pain

SENSORY MECHANISMS (GENERAL)

SEE SENSORY-PERCEPTUAL PROCESSES, SENSORY MECHANISMS (GENERAL)

SENSORY NERVES

SEE NERVOUS SYSTEM, AFFERENT NERVES

SENSORY-PERCEPTUAL DISORDERS, SENSORY DISORDERS

** P01DE-02872-12 0060 Craniofacial dysmorphology - Sensory deficits in otocraniofacial syndromes

SENSORY-PERCEPTUAL PROCESSES, BODY IMAGE

R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)

SENSORY-PERCEPTUAL PROCESSES, PAIN

SEE ALSO DENTAL PAIN

SEE ALSO NERVOUS DISORDERS PERIPHERAL, TRIGEMINAL NEURALGIA

SEE ALSO ORAL-FACIAL PAIN

SEE ALSO ORAL-PHARYNGEAL DISORDERS, MPD SYNDROME

SEE ALSO SENSORY DEPRESSION, ANALGESIA

** R13DE-05982-01 Third World Congress on Pain (Scotland)

SENSORY-PERCEPTUAL PROCESSES, PAIN TOLERANCE

** R01DE-04004-07 Acupuncture and perception of dental pain (human)

** R01DE-04976-04 Behavioral strategies for reducing dental avoidance (human)

SENSORY-PERCEPTUAL PROCESSES, PERCEPTION

SEE ALSO SENSORY-PERCEPTUAL PROCESSES, SIGNAL DETECTION

R01DE-04990-03 Normal and abnormal faces (human)

SENSORY-PERCEPTUAL PROCESSES, PROPRIOCEPTION

SEE ALSO EAR, LABYRINTH, VESTIBULAR APPARATUS

SEE ALSO MUSCLE FUNCTION, MUSCLE STRETCH (RECEPTORS)

SEE ALSO MUSCLE FUNCTION, MUSCLE STRETCH REFLEX

SEE ALSO SKELETAL MOVEMENT, BODY MOVEMENT

R01DE-04884-13 Neural processes in somatic movement (monkeys)

R23DE-05036-03 Nocturnal masseter muscle activity and jaw dysfunction (human)

SENSORY-PERCEPTUAL PROCESSES, SENSORY MECHANISMS (GENERAL)

SEE ALSO EYE, VISION

** R01DE-05208-03 Mechanism of dental and facial sensation (monkeys)

SENSORY-PERCEPTUAL PROCESSES, SIGNAL DETECTION

R01DE-04004-07 Acupuncture and perception of dental pain (human)

SENSORY-PERCEPTUAL PROCESSES, SOMESTHESIS**SENSORY-PERCEPTUAL PROCESSES, SOMESTHESIS**

SEE BRAIN, CEREBRAL CORTEX, SOMESTHETIC SENSORY AREA

SEE ALSO NERVOUS SYSTEM, AFFERENT NERVES, CUTANEOUS SENSORY NERVES

SEE ALSO SENSORY-PERCEPTUAL PROCESSES, PAIN

SEE ALSO SENSORY-PERCEPTUAL PROCESSES, PROPRIOCEPTION

SEE ALSO SENSORY-PERCEPTUAL PROCESSES, THERMORECEPTION

SEE ALSO SENSORY-PERCEPTUAL PROCESSES, TOUCH

** P50DE-02668-15 0204 Regional dental research center - Psychophysical measures of combined tactile and thermal sensitivity (human)

P50DE-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli

SENSORY-PERCEPTUAL PROCESSES, TASTE

N01DE-02427-04 Synthesize noncarcinogenic sweeteners

** R01DE-05728-01 Role of chemoreceptors in craniofacial function (lambs)

SENSORY-PERCEPTUAL PROCESSES, TASTE THRESHOLD

R01DE-05476-02 Novel peptide derived sweeteners

SENSORY-PERCEPTUAL PROCESSES, THERMORECEPTION

P50DE-02668-15 0204 Regional dental research center - Psychophysical measures of combined tactile and thermal sensitivity (human)

** P50DE-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli

R01DE-04786-04 Dental and orofacial pain-Brain stem mechanisms (cats)

SENSORY-PERCEPTUAL PROCESSES, TOUCH

P50DE-02668-15 0199 Regional dental research center - Mechanisms governing the behavior of somatosensory cerebral cortical neurons

P50DE-02668-15 0200 Regional dental research center - Response of first order mechanoreceptive afferents to moving tactile stimuli

** P50DE-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli

** P50DE-02668-15 0210 Regional dental research center - Somesthetic capacities of human subjects (monkeys)

R01DE-05558-01 Sensory alterations of craniofacial form (Rhesus monkeys)

SENSORY THRESHOLDS

SEE ALSO SENSORY DEPRESSION, ANALGESIA

SEE ALSO SENSORY-PERCEPTUAL PROCESSES, TASTE THRESHOLD

P50DE-02668-15 0204 Regional dental research center - Psychophysical measures of combined tactile and thermal sensitivity (human)

P50DE-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli

R01DE-05204-03 Operant neural control in trigeminal pain systems (rat)

SEPTAL DEFECT HEART

SEE CONGENITAL ABNORMALITIES, HEART SEPTAL DEFECTS

SEROLOGY

SEE IMMUNOLOGY, SEROLOGY*

SEROTONIN

SEE BENZOPYRROLES, SEROTONIN

SEROTYPES, SEROTYPING

SEE MICROBIAL IDENTIFICATION AND CLASSIFICATION, SEROTYPING

SERUM

SEE BLOOD AND RE SYSTEM, BLOOD, SERUM

SERUM PROTEINS

SEE BLOOD PROTEINS

SERVOMECHANISMS (NEURAL)

SEE INFORMATION PROCESSING AND CONTROL (NEURAL)

SET, MENTAL

SEE PSYCHOLOGY, ATTITUDES (AND RELATED)

SEX

SEE ALSO GENETIC DISORDERS, SEX-LINKED CONDITIONS

SEE ALSO REPRODUCTIVE HORMONES, SEX HORMONES

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

- P01DE-02847-13 0021 Microbial ecology and its relation to dental disease - Acquisition, transmission and localization of human oral bacteria (rodents)
 P01DE-03568-07 0008 Craniofacial anomalies--Etiology and treatment - Craniofacial growth

SEX, MALE

- SEE ALSO CHILD DEVELOPMENT, PUBERTY
 R01DE-04047-05 Extensibility characteristics of human cheek

SEX, SEX DIFFERENCE

- P50DE-02668-15 0213 Regional dental research center - Hormone action is the salivary glands of inbred mice
 P01DE-02872-12 0036 Craniofacial dysmorphology - Natural history of cleft lip and palate--Malocclusion
 P01DE-02872-12 0061 Craniofacial dysmorphology - Craniofacial dysmorphology
 P01DE-02872-12 0062 Craniofacial dysmorphology - Congenital palatopharyngeal incompetence
 R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)
 P01DE-03610-15 0017 Cranio-facial growth and development - Craniofacial profile patterns in normal and malformed prenatals and postnatals
 R01DE-04781-02 Serial craniofacial growth in clefting--Birth to fifteen years
 R01DE-05104-02 Periodontitis--Microbial etiology and prediction
 R01DE-05330-02 Herpes virus antibodies in patients with oral cancer
 R01DE-05410-02 Orthodontic treatment effects on craniofacial growth (human)
 R01DE-05505-02 Periodontitis and host defense in juvenile diabetes (human)
 R01DE-05669-01 Chorion type and dental morphology in twins
 R01DE-05698-01 Evaluation of orthognathic surgery patients
 R01DE-05868-01 Multivariate analysis of craniofacial growth in clefting
 R23DE-05942-01 Airway factors in cleft palate dentofacial deformity

SEX DIFFERENCE

- SEE SEX, SEX DIFFERENCE

SEX HORMONES

- SEE REPRODUCTIVE HORMONES, SEX HORMONES

SEX-LINKED CONDITIONS

- SEE GENETIC DISORDERS, SEX-LINKED CONDITIONS

SF ANTIGEN

- SEE GLYCOPROTEINS, FIBRONECTIN

SHIVERING

- SEE TEMPERATURE (BODY) REGULATION

SHUNTS, HEART SEPTAL DEFECTS

- SEE CONGENITAL ABNORMALITIES, HEART SEPTAL DEFECTS

SI

- SEE SILICON

SIALIC ACIDS

- SEE SUGAR ACIDS, SIALIC ACIDS

SIBLING ORDER, POSITION

- SEE FAMILY, SIBLING ORDER

SIDEROPHILIN

- SEE METALLOPROTEINS, TRANSFERRIN

SIGNAL DETECTION

- SEE SENSORY-PERCEPTUAL PROCESSES, SIGNAL DETECTION

SILANES

- ** R01DE-05224-01 Enamel silylation as a caries prevention method (human, animals)

SILICATES, GLASS

- R01DE-05353-04 Dental porcelains improvement with inorganic polymers
 R01DE-05460-02 Bonding of dental porcelain to non-precious alloys

SILICON

- R01DE-04252-07 Semi and nonprecious metal-porcelain systems

SILICON TETRAHYDRIDE

- SEE SILANES

SILVER (COMPOUNDS)

- SEE METALS, HEAVY METALS, SILVER (COMPOUNDS)

SINGLE CELL ANALYSIS

- SEE CELLS, SINGLE CELL ANALYSIS

SINGLE FILE PORE DIFFUSION

- SEE BIOLOGICAL TRANSPORT, PASSIVE TRANSPORT, DIFFUSION

SINGLE UNIT (CELL) ANALYSIS

- SEE CELLS, SINGLE CELL ANALYSIS

SINGLE UNIT TRAINING (AUTOGENIC)

- SEE PSYCHOLOGY, CONDITIONING, AUTOGENIC AND INTERNAL CONTROL

SINUSES (PARANASAL)

- SEE NASAL, PARANASAL SINUSES

SKELETAL DISORDERS, ANKYLOSIS

- R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)

SKELETAL DISORDERS, ARTHRITIS

- P50DE-02731-15 0001 Development support for dental research institute - Functional disturbances of the masticatory system (human)
 R01DE-03738-09 Humoral and cellular mediators of inflammation (human, animals)

SKELETAL DISORDERS, ARTHRITIS, OSTEOARTHRITIS

- ** R01DE-05351-02 Electron optical examination of mineralized tissues (animals)

SKELETAL DISORDERS, ARTHRITIS, RHEUMATOID

- SEE ALSO IMMUNOLOGY, ANTIGEN-ANTIBODY REACTIONS, IMMUNE COMPLEXES
 R01DE-05459-02 Phenytoin--Pathogenesis of gingival overgrowth (cats)

SKELETAL DISORDERS, BONE DEVELOPMENT

- SEE ALSO CONGENITAL ABNORMALITIES, FUSION FAILURES
 SEE ALSO CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL
 SEE ALSO CONGENITAL ABNORMALITIES, SKELETAL (GENERAL)
 SEE ALSO METABOLIC DISORDERS INBORN, MARFAN SYNDROME

SKELETAL DISORDERS, BONE DEVELOPMENT, IMPERFECTA

- SEE ALSO METABOLIC DISORDERS INBORN, OSTEOPEITROSIS
 SEE ALSO METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN
 ** P01DE-02872-12 0035 Craniofacial dysmorphology - Natural history of cleft lip and palate--Morphoanalysis
 P01DE-02872-12 0036 Craniofacial dysmorphology - Natural history of cleft lip and palate--Malocclusion
 ** R01DE-05198-02 Influences on vertical dento-facial growth (guinea pigs, children, adults)

SKELETAL DISORDERS, BONE DISORDERS (GENERAL)

- SEE ALSO KIDNEY DISORDERS, RENAL RICKETS
 R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)

SKELETAL DISORDERS, BONE METABOLISM (GENERAL)

- SEE ALSO CALCIUM (MINERAL) IMBALANCES
 SEE ALSO METABOLIC DISORDERS INBORN, EHLERS-DANLOS SYNDROME
 SEE ALSO METABOLIC DISORDERS INBORN, MARFAN SYNDROME
 SEE ALSO METABOLIC DISORDERS INBORN, MUCOPOLYSACCHARIDOSIS, LIPOCHONDRODYSSTROPHY
 SEE ALSO METABOLIC DISORDERS INBORN, OSTEOGENESIS IMPERFECTA
 SEE ALSO METABOLIC DISORDERS INBORN, OSTEOPEITROSIS
 SEE ALSO METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN

- R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
 P01DE-01850-18 0081 Nutritional sources and metabolic roles of fluoride - Effect of fluoride intake on strain N mice
 R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)

- ** P50DE-02668-15 0192 Regional dental research center - Skeletal actions of calcitonin in the rat
 R13DE-05752-01 Conference on biology of mineralized connective tissues

SKELETAL DISORDERS, BONE METABOLISM, OSTEOPOROSIS

- P50DE-02600-15 0028 Support for oral biology research center - Repletion and coupling in bone volume regulation (rat)

- P50DE-02670-15 0020 Institute of Dental Research - Nutrition--Disease proneness during dental development
 R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)

- ** R01DE-05351-02 Electron optical examination of mineralized tissues (animals)
 R01DE-06065-01 The role of lymphoid cells in alveolar bone resorption

SKELETAL DISORDERS, BONE RESORPTION ABNORMAL

- SEE ALSO SKELETAL DISORDERS, BONE METABOLISM, OSTEOPEITROSIS

- P50DE-02668-15 0192 Regional dental research center - Skeletal actions of calcitonin in the rat

- P50DE-02731-15 0037 Development support for dental research institute - Luminescence and polarized light in the diagnosis and treatment of caries

- ** R01DE-03420-09 Immune phenomena in experimental periodontal disease (rats)
 ** R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)

- ** R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)
 P50DE-04881-05 0001 Center for clinical research in periodontal diseases - Diagnosis and treatment of destructive periodontal diseases
 R01DE-05078-05 Craniofacial growth and remodeling (human)
 R01DE-05123-04 Periodontopathic bacteria:chemical-biologic nature (mammals)

- ** R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)
 ** R01DE-05255-03 Regulation of collagenase and bone resorption (chick embryos, mice)
 R23DE-05332-03 Bone in vitro--Ultrastructure and autoradiography (mice)
 ** R01DE-05413-02 Bone resorption in periodontal disease
 ** R01DE-05467-02 Pathogenesis of localized bone destruction
 R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)

SKELETAL DISORDERS, JOINT DISORDERS

- SEE ALSO METABOLIC DISORDERS INBORN, EHLERS-DANLOS SYNDROME

SKELETAL DISORDERS, JOINT DISORDERS, METABOLIC DISORDERS INBORN, MUCOPOLYSACCHARIDOSIS, LIPOCHONDRODYSSTROPHY

- SEE ALSO SKELETAL DISORDERS, ANKYLOSIS
 SEE ALSO SKELETAL DISORDERS, ARTHRITIS
 R01DE-04610-03 Physiological studies on mastication (human)

- R01DE-04889-04 Dental significance of jaw muscle silent periods (human)

- ** R01DE-05659-01 Surgical and radiographic evaluation of the temporomandibular joint (human)

SKELETAL DISORDERS, ORTHOPEDICS

- SEE ALSO DENTISTRY, ORTHODONTICS
 SEE ALSO ORAL-FACIAL RESTORATION
 R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
 R23DE-05883-01 Implants as anchors to move teeth and facial bones (dogs, monkeys)

SKELETAL DISORDERS, ORTHOPEDICS, ARTHROPLASTY

- R01DE-05659-01 Surgical and radiographic evaluation of the temporomandibular joint (human)

SKELETAL DISORDERS, ORTHOPEDICS, FRACTURE FIXATION

- R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)

SKELETAL DISORDERS, ORTHOPEDICS, LIMBS ARTIFICIAL

- R01DE-05292-03 Biological prosthetic attachment (dog)

SKELETAL DISORDERS, ORTHOTIC MATERIALS

- R13DE-05898-01 13th Annual International Biomaterials Symposium - 1981

SKELETAL DISORDERS, OSSIFICATION**SKELETAL DISORDERS, OSSIFICATION, PATHOLOGIC**

- SEE ALSO CALCIUM (MINERAL) IMBALANCES, CALCIFICATION
 PATHOLOGIC
 R01DE-04600-04 Hydroxyapatite remineralization--Role of fluoride

SKELETAL DISORDERS CONGENITAL

- SEE CONGENITAL ABNORMALITIES, SKELETAL (GENERAL)

SKELETAL DISORDERS DIAGNOSIS (INCL EXAMS)*

- SEE ALSO BODY PHYSICAL CHARACTERISTICS (GENERAL)
 SEE ALSO MUSCLE FUNCTION, ELECTROMYOGRAPHY*
 M P01DE-05837-01 Growth, surgical, and speech aspects of cleft palate

SKELETAL MOVEMENT, BODY MOVEMENT

- SEE ALSO MUSCLE FUNCTION, MUSCLE STRETCH REFLEX
 SEE ALSO ORAL-PHARYNGEAL, JAW MOVEMENT
 R01DE-05204-03 Operant neural control in trigeminal pain systems (rat)

SKELETAL MOVEMENT, HEAD MOVEMENT

- R01DE-05204-03 Operant neural control in trigeminal pain systems (rat)

SKELETAL MOVEMENT, POSTURE

- R01DE-05145-03 Adjustive cranial skeletal growth (rats)
 R01DE-05215-03 Influences on stability following orthognathic surgery

SKELETAL MUSCLE

- SEE MUSCLES, STRIATED MUSCLE

SKELETAL STRESS

- ** R01DE-04531-04 Strain in the facial bones of (primates)

SKELETAL SYSTEM, BONE

- ** R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)
 ** P01DE-01850-18 0088 Nutritional sources and metabolic roles of fluoride - Fluoride and glycosaminoglycans in bone (mice)

- ** P01DE-01850-18 0089 Nutritional sources and metabolic roles of fluoride - Effect of skeletal fluoride load on retention of administered fluoride

- ** P50DE-02600-15 0028 Support for oral biology research center - Repletion and coupling in bone volume regulation (rat)

- P50DE-02668-15 0176 Regional dental research center - Collagen biochemistry and the myeloblastosis associated virus infected cells

- ** R23DE-05332-03 Bone in vitro--Ultrastructure and autoradiography (mice)

(contd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
 See Appendix for investigator's name and Grant Number.

- R13DE-05752-01 Conference on biology of mineralized connective tissues

SKELETAL SYSTEM, BONE, PERIOSTEUM

- R01DE-05078-05 Craniofacial growth and remodeling (human)

SKELETAL SYSTEM, BONE CELLS

- P50DE-02600-15 0028 Support for oral biology research center - Repletion and coupling in bone volume regulation (rat)

- R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)

- ** R01DE-04345-06 Cellular and molecular aspects of mineralization (chick embryo)

- R23DE-05332-03 Bone in vitro—Ultrastructure and autoradiography (mice)

- R01DE-05351-02 Electron optical examination of mineralized tissues (animals)

SKELETAL SYSTEM, BONE CELLS, OSTEOBLASTS

- P50DE-02668-15 0176 Regional dental research center - Collagen biochemistry and the myeloblastosis associated virus infected cells

- R01DE-05109-02 Composite bone grafts in dentistry and medicine

- ** R01DE-05209-04 Metabolic pathways in bone

- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)

SKELETAL SYSTEM, BONE CELLS, OSTEOCLASTS

- SEE ALSO HYPERSENSITIVITY, LYMPHOKINES, OSTEOCLAST ACTIVATING FACTOR

- SEE ALSO SKELETAL SYSTEM, BONE RESORPTION-REMODELING PHYSIOLOGIC

- P50DE-02600-15 0028 Support for oral biology research center - Repletion and coupling in bone volume regulation (rat)

- R01DE-03745-10 Ultrastructure of experimental periodontitis (rats)

- ** R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)

- ** R01DE-04345-06 Cellular and molecular aspects of mineralization (chick embryo)

- ** R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)

- R01DE-04844-04 Stress-related bone resorption—Mechanisms of action (rats)

- P50DE-04898-05 0001 Periodontal disease research center - Microbiology (human)

- R01DE-05049-01 Saliva-complement interactions and oral mucosal defense

- ** R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)

- R01DE-05188-03 Blood vessel response in periodontal disease (dogs, rats)

- ** R01DE-05209-04 Metabolic pathways in bone

- R01DE-05413-02 Bone resorption in periodontal disease

- R01DE-05494-02 Activation of macrophages in periodontal disease

- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)

- R01DE-05996-01 Alveolar bone metabolism during tooth eruption (Dogs)

- ** R01DE-06065-01 The role of lymphoid cells in alveolar bone resorption

SKELETAL SYSTEM, BONE DEVELOPMENT

- SEE ALSO METABOLIC DISORDERS INBORN, EHLERS-DANLOS SYNDROME

- ** R01DE-02873-14 Facial and dental growth in pre- and post-adolescents (twins)

- M P01DE-03568-07 Craniofacial anomalies—Etiology and treatment

- ** R01DE-03568-07 0008 Craniofacial anomalies—Etiology and treatment - Craniofacial growth

- M P01DE-03610-15 Cranio-facial growth and development

- ** R01DE-03610-15 0016 Cranio-facial growth and development - Craniofacial shape change and oral development

- ** R01DE-03610-15 0017 Cranio-facial growth and development - Craniofacial profile patterns in normal and malformed prenatals and postnates

- ** R01DE-03610-15 0018 Cranio-facial growth and development

- R01DE-03794-09 Surgical-orthodontics and bone healing (monkeys)

- R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)

- R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)

- ** R23DE-05037-03 Biochemical role of zinc in teeth and bones

- ** R01DE-05078-05 Craniofacial growth and remodeling (human)

- ** R01DE-05145-03 Adjustive cranial skeletal growth (rats)

- ** R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)

- ** R01DE-05397-01 Craniofacial bone formation and muscle activity (Rhesus monkey)

- ** R01DE-05574-01 Neural aspects of craniofacial morphogenesis (frogs)

- R23DE-05627-02 Effects of mechanical forces on craniofacial growth (monkeys, rabbits)

- P01DE-05837-01 0002 Growth, surgical, and speech aspects of cleft palate - Maxillofacial growth (dogs, tamarins)

- ** R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

SKELETAL SYSTEM, BONE DEVELOPMENT, OSTEOGENESIS

- SEE ALSO METABOLIC DISORDERS INBORN, OSTEOGENESIS IMPERFECTA

- SEE ALSO SKELETAL SYSTEM REGENERATION, BONE REGENERATION

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)

- P01DE-02848-11 0003 Biology of connective tissue, bones, and teeth - Mandibular morphogenesis—Embryonic neonatal and postnatal development (mice)

- ** R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)

- ** R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)

SKELETAL SYSTEM, BONE DEVELOPMENT, OSSIFICATION NORMAL

- SEE ALSO CALCIUM (MINERAL) BALANCE, CALCIFICATION PHYSIOLOGIC

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)

- R01DE-02525-16 Ultrastructural histopathology of human dental enamel

- ** P50DE-02623-14 0030 Center for oral health research - Role of mitochondria in the mineralization process (chickens)

- P50DE-02668-15 0151 Regional dental research center - Factors controlling the flux of ions into developing enamel

- M P50DE-02670-15 0003 Institute of Dental Research

- ** P50DE-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues

- ** P50DE-02731-15 0036 Development support for dental research institute - Optimal methods of enamel remineralization

- ** R01DE-03223-11 Kinetics of mineralization of teeth (human)

- ** R01DE-04141-07 Mechanism of hard tissue mineralization (human, rats)

- ** R01DE-04345-06 Cellular and molecular aspects of mineralization (chick embryo)

- R01DE-04385-06 Mechanism of dental caries (human)

- R01DE-04475-04 Mineral nutrition and alveolar bone loss (mice)

- ** R01DE-04600-04 Hydroxyapatite remineralization—Role of fluoride

- R01DE-04819-05 Remineralization of enamel caries in vitro (human)

- ** R01DE-05351-02 Electron optical examination of mineralized tissues (animals)

- ** R01DE-05487-02 Kinetics of mineral recycling in teeth and bone

- ** R23DE-05491-02 Control of biomineralization in two species (snails)

- ** R13DE-05752-01 Conference on biology of mineralized connective tissues

SKELETAL SYSTEM, BONE RESORPTION-REMODELING PHYSIOLOGIC

- SEE ALSO SKELETAL SYSTEM, BONE CELLS, OSTEOCLASTS

- ** P50DE-02600-15 0028 Support for oral biology research center - Repletion and coupling in bone volume regulation (rat)

- R01DE-03598-07 Dentofacial effects of forces to retract the maxilla (human)

- R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)

- ** R01DE-03818-08 Role of the osteoclast in tooth eruption (rats)

- ** R01DE-04345-06 Cellular and molecular aspects of mineralization (chick embryo)

- P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)

- ** R01DE-05078-05 Craniofacial growth and remodeling (human)

- R01DE-05136-03 Osteoclast origin and histogenesis in periodontium (rats)

- ** R01DE-05209-04 Metabolic pathways in bone

- R01DE-05381-01 Temporomandibular joint changes in young adults

- ** R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)

- R01DE-05397-01 Craniofacial bone formation and muscle activity (Rhesus monkey)

- ** R01DE-05412-02 Electric current, bone remodeling and tooth movement (cats)

- R01DE-05487-02 Kinetics of mineral recycling in teeth and bone

- R01DE-05494-02 Activation of macrophages in periodontal disease

- R01DE-05512-02 Role of macrophages in periodontal disease

- ** R01DE-05558-01 Sensory alterations of craniofacial form (Rhesus monkeys)

- R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)

- R23DE-05967-01 Role of prostaglandin E in periodontal disease activity

- ** R01DE-06065-01 The role of lymphoid cells in alveolar bone resorption

SKELETAL SYSTEM, CARTILAGE

- P50DE-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues

- ** P50DE-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues

- R01DE-05351-02 Electron optical examination of mineralized tissues (animals)

SKELETAL SYSTEM, CARTILAGE CELLS

- P50DE-02731-15 0031 Development support for dental research institute - Chemistry and physiology of proteoglycans and collagen of connective tissues

- R01DE-04327-06 Mechanical and electrical effects on osteogenesis (chick embryo)

- R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

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- R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

- R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

(contd).

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**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

SK**SKELETAL TISSUE PROSTHESIS, BONE**

SEE ALSO DENTAL PROSTHESIS

SEE ALSO ORAL-FACIAL RESTORATION, CLEFT PALATE PROSTHESIS

SEE ALSO SKELETAL DISORDERS, ORTHOPEDICS, LIMBS ARTIFICIAL

- ** R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate
- ** R01DE-05292-03 Biological prosthetic attachment (dog)

SKELETAL TISSUE TRANSPLANTATION, BONE

R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)

- ** P01DE-02872-12 0053 Craniofacial dysmorphology - Maxillofacial prosthetics (human)

R01DE-03794-09 Surgical-orthodontics and bone healing (monkeys)

R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)

- ** R01DE-05109-02 Composite bone grafts in dentistry and medicine

SKIN (GENERAL)

SEE ALSO ALBUMINOID, KERATIN

SEE ALSO ALBUMINOID, KERATOHYALIN

SEE ALSO GROWTH FACTORS (INCL. ANABOLICS), EPIDERMAL GROWTH FACTOR

- ** P50DE-02600-15 0032 Support for oral biology research center - Keratohyalin in keratinization of oral mucosa and skin (human, rats)

- ** P50DE-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli

P50DE-02670-15 0003 Institute of Dental Research - Biochemistry of collagenous and noncollagenous proteins of connective tissues

R01DE-03318-10 The molecular nature of gingival and mucosal collagen (rat)

- ** R01DE-04660-06 Keratohyalin in keratinization-Oral mucosa and skin (human)

R01DE-04990-03 Normal and abnormal faces (human)

R01DE-05190-03 Factors determining variation in adult oral mucosa

R23DE-05393-03 Factors association with hyperplasia of oral mucosa

R01DE-05404-03 Dental pain-Trigeminal nucleus caudalis (cats)

SKIN DISORDERS, ERYTHEMA

SEE ALSO CONNECTIVE TISSUE DISORDERS, LUPUS

ERYTHEMATOSUS SYSTEMIC

- R23DE-05967-01 Role of prostaglandin E in periodontal disease activity

SKIN DISORDERS, KELOID

SEE ALSO INJURIES, SCARS

- R01DE-05459-02 Phenytoin-Pathogenesis of gingival overgrowth (cats)

SKIN DISORDERS, PEMPHIGUS

R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)

SKIN DISORDERS, SKIN KERATOSIS

R01DE-05255-02 Nature of the permeability barrier in oral epithelium

SKIN DISORDERS, VESICULAR (GENERAL)

R01DE-04338-06 Characterization of oral mucosa and skin basal lamina (human, animals)

SKIN INFECTIONS

R23DE-05572-02 NEW antiviral therapy for oral and other herpes (mice, guinea pig, rabbits)

SKIN NEOPLASMS

SEE NEOPLASMS OF SKIN

SKULL

SEE SKELETAL SYSTEM, SKULL

SKULL ABNORMALITIES

SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL

SL-A LOCUS (PIG)

SEE IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)

SLEEP

SEE PSYCHIC ACTIVITY LEVEL, SLEEP

SLOW RELEASE PREPARATIONS (DRUGS)

SEE DRUGS, SLOW RELEASE PREPARATIONS

SLOW VIRUS DISEASES

SEE VIRUS DISEASE CHARACTERISTICS, LATENT DORMANT OR SLOW

SMALL LYMPHOCYTE DEPENDENT IMMUNE SYSTEM

SEE IMMUNITY, CELLULAR IMMUNITY (GENERAL)

SMOKING TOBACCO

SEE PSYCHOLOGY, HABITS, SMOKING

SMOLDERING VIRUS DISEASES

SEE VIRUS DISEASE CHARACTERISTICS, LATENT DORMANT OR SLOW

SN

SEE METALS, HEAVY METALS, TIN (COMPOUNDS)

SO ANTIGEN

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

SOCIAL ADJUSTMENT

SEE PSYCHOLOGY SOCIAL, SOCIAL ADJUSTMENT

SOCIAL GROUPS, ETHNIC

R01DE-05684-01 Saliva proteins-Chemistry, genetics and oral health

SOCIAL GROUPS, ETHNIC, AMERICANS, BLACK AMERICANS

R01DE-05078-05 Craniofacial growth and remodeling (human)

SOCIAL GROUPS, RACIAL STOCKS

P01DE-02872-12 0061 Craniofacial dysmorphology - Craniofacial dysmorphology

P01DE-03610-15 0017 Cranio-facial growth and development - Craniofacial profile patterns in normal and malformed prenatals and postnates

SOCIAL PSYCHOLOGY

SEE PSYCHOLOGY SOCIAL (SEE ALSO SOCIAL...)

SOCIOECONOMICS

R01DE-05511-02 Evanston-Oak park fluoridation study after 25 years (human)

N01DE-82413-05 Long-term effect of orthodontic treatment

SOCIOENVIRONMENT

SEE ALSO FAMILY

R23DE-05497-02 Dental disease and work loss (human)

SOCIOENVIRONMENT, RURAL AREAS

N01DE-92421-14 National caries prevalence survey

SOCIOENVIRONMENT, URBAN AREAS

N01DE-92421-14 National caries prevalence survey

SODIUM

R01DE-05354-04 Prevention of dental caries (rats, human)

R01DE-05375-01 Surface composition of biological apatites

R01DE-05483-02 Characterization of predentinal extracellular fluid (rats)

SODIUM-POTASSIUM PUMP

SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS, SODIUM-POTASSIUM PUMP

SODIUM PUMP

SEE BIOLOGICAL TRANSPORT, ACTIVE TRANSPORT, ION PUMPS, SODIUM PUMP

SODIUM SALICYLATE

SEE PHENYL CARBOXYLATES, SALICYLATES

SOLS

SEE PHYSICAL PROPERTIES, COLLOIDS, SOLS

SOLUBILITY

SEE PHYSICAL PROPERTIES, SOLUBILITY

SOLVENTS

SEE PHYSICAL PROPERTIES, SOLVENTS

SOMATESTHESIA

SEE SENSORY-PERCEPTUAL PROCESSES, SOMESTHESIS

SOMATIC ANTIGENS, NONMICROBIAL

SEE IMMUNOLOGY, ANTIGENS, SURFACE ANTIGENS (GENERAL)

SOMATIC REFLEXES

SEE NEUROPHYSIOLOGY, REFLEX, SOMATIC REFLEXES

SOMATOLOGY (GENERAL)

SEE BODY PHYSICAL CHARACTERISTICS (GENERAL)

SOMATOSENSORY MOTOR SYSTEM (GENERAL)

SEE NEUROMOTOR SYSTEM, SENSORIMOTOR SYSTEMS (GENERAL)

SOMATOSTATIN

SEE PITUITARY-DIENCEPHALON HORMONES, SOMATOSTATIN

SOMATOTROPIN RELEASE-INHIBITING FACTOR

SEE PITUITARY-DIENCEPHALON HORMONES, SOMATOSTATIN

SOMESTHESIS

SEE SENSORY-PERCEPTUAL PROCESSES, SOMESTHESIS

SOMESTHETIC SENSORY AREA

SEE BRAIN, CEREBRAL CORTEX, SOMESTHETIC SENSORY AREA

SOMNIFACIENTS

SEE PSYCHOPHARMACOLOGICAL AGENTS, HYPNOTICS AND SEDATIVES

SOPORIFICS

SEE PSYCHOPHARMACOLOGICAL AGENTS, HYPNOTICS AND SEDATIVES

SORBITOL

SEE SUGAR ALCOHOLS, HEXITOLS, D-GLUCITOL

SORBITOL-XYLITOL DEHYDROGENASE

SEE OXIDOREDUCTASES, SORBITOL-XYLITOL DEHYDROGENASE

SOUND

SEE PHYSICAL PROPERTIES, SOUND

SPECIES

SEE BIOLOGY, SYSTEMATIC, SPECIES

SPECIFIC GRAVITY

SEE PHYSICAL PROPERTIES, DENSITY (SPECIFIC GRAVITY)

SPEECH

SEE INFORMATION-COMMUNICATION BEHAVIOR, SPEECH

SPEECH DISORDERS

SEE INFORMATION-COMMUNICATION DISORDERS, SPEECH DISORDERS

SPEECH DISORDERS DIAGNOSIS

SEE INFORMATION-COMMUNICATION DISORDERS, SPEECH DISORDERS DIAGNOSIS

SPEECH THERAPY

SEE INFORMATION-COMMUNICATION DISORDERS, SPEECH THERAPY

SPINAL NERVES

SEE NERVOUS SYSTEM, SPINAL NERVES

SPIRAL AND CURVED BACTERIA

SEE BACTERIA, PSEUDOMONADALES, SPIRILLACEAE*

SEE BACTERIA, PSEUDOMONADALES, VIBRIO*

SPIRILLACEAE

SEE BACTERIA, PSEUDOMONADALES, SPIRILLACEAE*

SPIROCHETES

SEE BACTERIA, SPIROCHETES*

SPLEEN

SEE BLOOD AND RE SYSTEM, SPLEEN

SPlicing, GENE (GENETIC MANIPULATION)

SEE GENETIC MANIPULATION

SPREADING FACTOR

SEE CARBOHYDRASES, HYALURONIDASE

SQUAMOUS CELL CARCINOMA

SEE NEOPLASMS, CARCINOMA EPIDERMOID

SR

SEE METALS, ALKALINE EARTH METALS, STRONTIUM (COMPOUNDS)

STAGING, NEOPLASMS

SEE NEOPLASMS CLASSIFICATION AND STAGING

STANDARDIZATION

SEE BIOLOGICAL PREPARATIONS AND STANDARDIZATION

SEE FOOD SCIENCES AND TECHNOLOGY, FOOD QUALITY-STANDARDS

SEE TISSUE (CELL) CULTURE, CELL CULTURE COLLECTIONS

BANKS AND REGISTRIES

STANDARDS FOR HEALTH CARE QUALITY

SEE HEALTH CARE QUALITY

STANDARDS FOR INFORMATION GATHERING METHODS (GENERAL)

SEE INFORMATION GATHERING METHODS EVALUATION-STANDARDS

STANNOUS FLUORIDE

SEE HALOGENS, FLUORINE (COMPOUNDS) SEE ALSO SPECIFICS

STARCH

SEE HEXOSANS, GLUCANS, STARCH

STARVATION

SEE NUTRITIONAL ABNORMALITIES, STARVATION

STATISTICAL MODELS

SEE MODELS, MATHEMATICAL

STATISTICS

SEE MATHEMATICS, STATISTICS (INCLUDING BIOMETRY)

STATUS DYSRAPHICUS

SEE CONGENITAL ABNORMALITIES, FUSION FAILURES

STEATORRHEA, CONGENITAL PANCREATIC

SEE METABOLIC DISORDERS INBORN, CYSTIC FIBROSIS

STEREOPHOTOGRAPHY

SEE OPTICS, PHOTOGRAPHY, STEREOPHOTOGRAPHY*

STEROID HORMONES

SEE ENDOCRINOLOGY, HORMONES, STEROID HORMONES

STEROID HORMONES METABOLISM

SEE ENDOCRINOLOGY, HORMONES METABOLISM, STEROID HORMONES METABOLISM

STEROID METABOLISM

SEE ALSO ENDOCRINOLOGY, HORMONES METABOLISM, STEROID HORMONES METABOLISM

- ** P50DE-02668-15 0213 Regional dental research center - Hormone action is the salivary glands of inbred mice

- ** R01DE-04039-04 Sex steroid metabolism in oral tissues

STEROIDS

SEE ALSO ENDOCRINOLOGY, HORMONES, STEROID HORMONES

R01DE-05322-01 Genetic analysis of birth defects involving

septa (human, mice)

- ** R23DE-05592-02 Biochemical mechanism of steroid-induced

clefting (mice)

STIMULANTS, GROWTH

SEE GROWTH FACTORS (INCL. ANABOLICS)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.
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 See Appendix for investigator's name and Grant Number.

(contd.)

STIMULANTS, MUSCLE

SEE MUSCLE STIMULANTS

STIMULATION, CHEMICAL

SEE DRUGS, PHARMACOLOGY, STIMULATION, CHEMICAL

STIMULUS INTERVAL

R01DE-04889-04 Dental significance of jaw muscle silent periods (human)

STIMULUS-RESPONSE (GENERAL)SEE ALSO ELECTROPOTENTIALS, EVOKED POTENTIALS
SEE ALSO ELECTROSTIMULUS
SEE ALSO TEMPERATURE, HEAT, CALORIC STIMULATION
R01DE-05208-03 Mechanism of dental and facial sensation (monkeys)**STOICHIOMETRY**

SEE CHEMISTRY, STOICHIOMETRY

STOMATITIS

SEE ORAL-PHARYNGEAL DISORDERS, STOMATITIS

STOMATITIS, APHTHOUS

SEE ORAL-PHARYNGEAL DISORDERS, STOMATITIS, APHTHOUS

STRATUM CORNEUM (EPIDERMIS)

SEE SKIN (GENERAL)

STREPTOCOCCACEAE

SEE BACTERIA, STREPTOCOCCACEAE*

STREPTOCOCCAL VACCINE

SEE VACCINES, BACTERIAL, STREPTOCOCCAL VACCINES

STREPTOCOCCUS

SEE BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS*

STREPTOCOCCUS GROUP A

SEE BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS GROUP A*

STREPTOCOCCUS HEMOLYTICUS (S.PYOGENES)

SEE BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS GROUP A*

STREPTOCOCCUS MITIS

SEE BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS MITIS*

STREPTOCOCCUS MUTANS

SEE BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS MUTANS*

STREPTOCOCCUS PYOGENES (S. HEMOLYTICUS)

SEE BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS GROUP A*

STREPTOCOCCUS SALIVARIUS

SEE BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS SALIVARIUS*

STREPTOCOCCUS SANGUIS

SEE BACTERIA, STREPTOCOCCACEAE, STREPTOCOCCUS SANGUIS*

STRESS BIOLOGICAL, PHYSIOLOGICAL

SEE ENVIRONMENT, STRESS

STRESS MECHANICAL

SEE ENVIRONMENT, STRESS MECHANICAL

STRESS PSYCHOLOGIC

SEE PSYCHOLOGIC STRESS

STRETCH RECEPTORS

SEE MUSCLE FUNCTION, MUSCLE STRETCH (RECEPTORS)

STRETCH REFLEX

SEE MUSCLE FUNCTION, MUSCLE STRETCH REFLEX

STRIATED MUSCLE

SEE MUSCLES, STRIATED MUSCLE

STROMA, CELL

SEE CELL COMPONENTS, CELL STROMA

STRONTIUM (COMPOUNDS)

SEE METALS, ALKALINE EARTH METALS, STRONTIUM (COMPOUNDS)

STRUCTURAL CHEMISTRY

SEE CHEMICAL STRUCTURE

STRUCTURE OF CARBOHYDRATES

SEE CARBOHYDRATES STRUCTURE

STRUCTURE OF PROTEINS-PEPTIDES

SEE PROTEINS-PEPTIDES STRUCTURE

STUART FACTOR

SEE BLOOD COAGULATION, FACTOR X

STYRENE POLYMERS

SEE PLASTICS, STYRENE POLYMERS

SUBGINGIVAL CURETTAGE

SEE DENTISTRY, SUBGINGIVAL CURETTAGE

SUBLINGUAL GLAND

SEE ORAL-PHARYNGEAL, SALIVARY GLANDS, SUBLINGUAL

SUBMANDIBULAR GLAND

SEE ORAL-PHARYNGEAL, SALIVARY GLANDS, SUBMANDIBULAR

SUBMAXILLARY GLAND

SEE ORAL-PHARYNGEAL, SALIVARY GLANDS, SUBMANDIBULAR

SUBSTANCE P (STEROID)

SEE PREGNANE SERIES 5ALPHA, 5ALPHA-PREGNANE-3BETA,17ALPHA,21-TRIOL-20-DNE

SUBSTITUTION REACTIONS (CHEMISTRY)

SEE CHEMICAL REACTIONS, SUBSTITUTION

SUCRASE

SEE CARBOHYDRASES, BETA-FRUCTOFURANOSIDASE

SUCROSE

SEE DISACCHARIDES, SUCROSE

SUCROSE ALPHA-D-GLUCOHYDROLASE

SEE CARBOHYDRASES, BETA-FRUCTOFURANOSIDASE

SUGAR ACIDS, MURAMIC ACID

R01DE-05494-02 Activation of macrophages in periodontal disease

SUGAR ACIDS, SIALIC ACIDS

R01DE-05632-01 Development of salivary gland secretory function (rats)

SUGAR ALCOHOLS, HEXITOLS, D-GLUCITOL

N01DE-02427-04 Synthesize noncariogenic sweeteners

SUGAR TRANSPORT

SEE CARBOHYDRATES TRANSPORT (GENERAL)

SUGARS, DIETARY

SEE NUTRITION, DIETARY CONSTITUENTS, DIETARY CARBOHYDRATES

SULFATASES, ARYLSULFATASES

R23DE-05424-03 Quantitative studies of lysosomes in amelogenesis (rats)

SULFATION

R01DE-05666-01 Biochemistry of salivary lipids (monkeys, rats, human)

SULFENIC ACIDS

R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)

SULFHYDRYLS

R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)

SULFIDES, DISULFIDESSEE ALSO CHEMICAL BONDS, DISULFIDE BONDS
N01DE-02427-04 Synthesize noncariogenic sweeteners**SULFINIC ESTERS**

SEE SULFONES

SULFONAMIDES

R01DE-05476-02 Novel peptide derived sweeteners

SULFONES

N01DE-02427-04 Synthesize noncariogenic sweeteners

SULFUR AMINO ACIDS, CYSTEINE

R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)

SULTHIAME

SEE SULFONAMIDES

SUNLIGHT

SEE RADIATION, ELECTROMAGNETIC WAVES, ULTRAVIOLET RAYS (290NM TO 380NM)

SUPEROXIDE

SEE OXIDES, SUPEROXIDE

SUPPRESSOR T LYMPHOCYTES

SEE BLOOD CELLS, T LYMPHOCYTES, SUPPRESSOR

SURFACE ACTIVE AGENTS

SEE PHYSICAL PROPERTIES, SURFACTANTS

SURFACE ACTIVITY, CELLULAR

SEE MEMBRANE SURFACE (BIOLOGICAL) ACTIVITY (GENERAL)

SURFACE ANTIGENS

SEE IMMUNOLOGY, ANTIGENS, SURFACE ANTIGENS (GENERAL)

SURFACE PROPERTIES (GENERAL)

SEE PHYSICAL PROPERTIES, SURFACE PROPERTIES (GENERAL)

SURFACTANTS

SEE PHYSICAL PROPERTIES, SURFACTANTS

SURGERYSEE ALSO EYE SURGERY
SEE ALSO NEOPLASMS SURGERY
SEE ALSO NEUROSURGERY
SEE ALSO ORAL-FACIAL RESTORATION
SEE ALSO ORAL SURGERY
SEE ALSO PARATHYROIDECTOMY
SEE ALSO SKELETAL DISORDERS, ORTHOPEDICS
SEE ALSO SKELETAL SYSTEM, SKULL, CRANIOTOMY
SEE ALSO TEMPERATURE (BODY), HYPOTHERMIA INDUCED, CRYOSURGERY
SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION
** R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)**SURGERY, MICROSURGERY AND MICRODISSECTION**

R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)

SURGERY, PLASTIC

SEE ALSO ORAL-FACIAL RESTORATION

** P01DE-02872-12 0038 Craniofacial dysmorphology - Evaluation of craniofacial surgery
P01DE-02872-12 0053 Craniofacial dysmorphology - Maxillofacial prosthetics (human)
R01DE-04517-03 Pin-retained prosthesis with surgery in cleft palate
R01DE-04990-03 Normal and abnormal faces (human)
R01DE-05371-01 Psychosocial evaluation of craniofacial patients
R01DE-05396-02 Craniofacial adaptations after maxillary osteotomy (monkeys)**SURGERY, POSTOPERATIVE**SEE ALSO DISEASES, COMPLICATIONS, POSTOPERATIVE
R01DE-04890-03 Plaque control-healing following periodontal surgery
R01DE-05203-03 Speech adaptations to orthognathic surgery (human)
R01DE-05582-01 Computer graphic analysis of cranio-facial morphology
R01DE-05744-01 Psychosocial factors in orthognathic surgery (human)
P01DE-05837-01 0001 Growth, surgical, and speech aspects of cleft palate - Speech pathology (human)
P01DE-05837-01 0002 Growth, surgical, and speech aspects of cleft palate - Maxillofacial growth (dogs, tamarins)
** P01DE-05837-01 0004 Growth, surgical, and speech aspects of cleft palate - Surgery (human, animals)**SURGERY, PREOPERATIVE**

R01DE-04990-03 Normal and abnormal faces (human)

SURGERY AND BIOENGINEERING STUDY SECTION

** R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

SURGERY STUDY SECTION

SEE SURGERY AND BIOENGINEERING STUDY SECTION

SURGICAL WOUNDS

SEE INJURIES, SURGICAL WOUNDS

SURVEYS, DENTAL (HEALTH)

SEE POPULATION SURVEYS, HEALTH SURVEYS, DENTAL

SURVEYS, POPULATION

SEE POPULATION SURVEYS

SUTURES

SEE SKELETAL SYSTEM, SKULL, CRANIAL SUTURES

SWALLOWING

SEE GASTROINTESTINAL FUNCTION, DEGLUTITION

SWEETENING AGENTS

SEE FOOD, SWEETENING AGENTS

SYMPATHETIC NERVOUS SYSTEM

SEE NERVOUS SYSTEM AUTONOMIC, SYMPATHETIC NERVOUS SYSTEM

SYMPATHOLYTIC AGENTS

SEE NEUROPHARMACOLOGICAL AGENTS, SYMPATHOLYTIC

SYMPATHOMIMETIC AGENTS

SEE NEUROPHARMACOLOGICAL AGENTS, SYMPATHOMIMETIC

SYMPOSIA

SEE INFORMATION DISSEMINATION, MEETINGS CONFERENCES SYMPOSIA

SYNAPSES

SEE NERVOUS SYSTEM, NERVE ENDINGS, SYNAPSES

SYNAPTIC RECEPTORS

SEE NEUROTRANSMITTERS RECEPTORS

SYNCHRONOUS CELL DIVISION

SEE CELL DIVISION, SYNCHRONOUS CELL DIVISION

SYNERGISMSEE DRUGS AND PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION
SEE DRUGS INTERACTION
SEE PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION (BIOLOGICAL AND ECOLOGICAL)**SYNSTOSES, CRANIAL**

SEE CONGENITAL ABNORMALITIES, ORAL-FACIAL-CRANIAL, CRANIOSYNOSTOSES

SYNOVIAL FLUID

SEE SKELETAL SYSTEM, SYNOVIAL FLUID

SYNTHESIS (ORGANIC)

SEE CHEMICAL SYNTHESIS, DESIGN AND PRODUCTION (GENERAL)

SYNTHESIS OF DRUGS

SEE DRUGS SYNTHESIS, DESIGN AND PRODUCTION

SYNTHETIC FOODS

SEE FOOD SCIENCES AND TECHNOLOGY, SYNTHETIC FOODS (contd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

SYSTEMATIC BIOLOGY

SEE BIOLOGY, SYSTEMATIC

T GENE

SEE IMMUNOGENETICS, HISTOCOMPATIBILITY GENES

TACTILE PERCEPTION

SEE SENSORY-PERCEPTUAL PROCESSES, TOUCH

TASTE

SEE SENSORY-PERCEPTUAL PROCESSES, TASTE

TASTE THRESHOLD

SEE SENSORY-PERCEPTUAL PROCESSES, TASTE THRESHOLD

TAXONOMY

SEE BIOLOGY, SYSTEMATIC

TEETH

SEE DENTAL STRUCTURE, TOOTH

TEFLON

SEE PLASTICS, FLUOROCARBON POLYMERS

TEICHOIC ACID

SEE POLYSACCHARIDES, TEICHOIC ACID

TEMPERAMENT

SEE PSYCHOLOGY, PERSONALITY

TEMPERATURE (SEE ALSO THERM...)

SEE ALSO SENSORY-PERCEPTUAL PROCESSES, THERMORECEPTION

R23DE-05519-02 Oxidation behavior of Ni-base crown and bridge alloys

TEMPERATURE, COLD

R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

TEMPERATURE, HEAT

SEE ALSO SENSORY-PERCEPTUAL PROCESSES, THERMORECEPTION

R01DE-05636-01 Cellular mediators in tooth maintenance and repair (rats)

R01DE-05640-01 Cytotoxicity of periodontopathic bacteria

TEMPERATURE, HEAT, CALORIC STIMULATION

** P50DE-02668-15 0204 Regional dental research center - Psychophysical measures of combined tactile and thermal sensitivity (human)

** P50DE-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli

TEMPERATURE (BODY)

P01DE-02872-12 0060 Craniofacial dysmorphism - Sensory deficits in oculo-craniofacial syndromes

TEMPERATURE (BODY), HYPOTHERMIA INDUCED, CRYOSURGERY

** R01DE-03991-06 Cryosurgical techniques applied to malignant melanoma

TEMPERATURE (BODY) REGULATION

P50DE-02668-15 0208 Regional dental research center - Effects of skin warming on neural responses to tactile stimuli

TEMPERATURE SENSE

SEE SENSORY-PERCEPTUAL PROCESSES, THERMORECEPTION

TEMPOROMANDIBULAR JOINT

SEE ORAL-PHARYNGEAL, JAW, TEMPOROMANDIBULAR JOINT

TENSILE STRENGTH

SEE PHYSICAL PROPERTIES, TENSILE STRENGTH

TENSOR TYMPANI

SEE MUSCLES, EAR MUSCLES, TENSOR TYMPANI

TEORELL MEMBRANE OSCILLATOR

SEE BIOLOGICAL TRANSPORT, MEMBRANE PERMEABILITY AND TRANSPORT

TERATOGENIC AGENTS

SEE CONGENITAL ABNORMALITIES, TERATOGENIC AGENTS

TESTING OF BIOMATERIALS

SEE BIOMATERIALS, BIOMATERIALS EVALUATION

TESTING OF INSTRUMENTATION, CLINICALLY ORIENTED

SEE BIOMEDICAL ENGINEERING, INSTRUMENTATION CLINICALLY ORIENTED

TESTOSTERONE

SEE ANDROSTANE SERIES, TESTOSTERONE

TESTS

SEE GENETICS, MUTAGENS, MUTAGEN TESTS

SEE HYPERSENSITIVITY TESTS

SEE IMMUNOLOGICAL TESTS AND IMMUNOASSAY, IMMUNOLOGICAL TESTS*

TETRACYCLINE

SEE ANTIBIOTICS, TETRACYCLINE

THALAMUS

SEE BRAIN, THALAMUS

THEOPHYLLINE

SEE PURINES, XANTHINES, THEOPHYLLINE

THERAPEUTIC EQUIVALENCE OF DRUGS

SEE DRUGS, PHARMACOLOGY, BIOAVAILABILITY

THERAPY, ACUPUNCTURE

** R01DE-04004-07 Acupuncture and perception of dental pain (human)

THERAPY, LAVAGE

N01DE-12433-00 Phase contrast evaluation of subgingival plaque (human)

THERAPY, PLACEBO EFFECT

R01DE-05369-03 Factors affecting dental postoperative pain

THERAPY, RELAXATION

SEE PSYCHIC ACTIVITY LEVEL, RELAXATION

THERAPY COMPLIANCE

** R23DE-05799-01 Behavioral methods for pedodontic management (human)

THERAPY EVALUATION

P01DE-01697-19 0039 A research program in craniofacial problems - Otitis media and its consequences (human)

** P50DE-02600-15 0041 Support for oral biology research center - Perio treatment (human)

** P50DE-02731-15 0033 Development support for dental research institute - Clinical trials of periodontal therapy

** P01DE-02872-12 0038 Craniofacial dysmorphism - Evaluation of craniofacial surgery

** R01DE-03497-09 Artificial tooth roots (Rhesus monkeys, human)

M P01DE-03568-07 Craniofacial anomalies-Etiology and treatment

** R01DE-03598-07 Dentofacial effects of forces to retract the maxilla (human)

R01DE-04358-06 Treatment of temporomandibular joint pain

R01DE-04494-05 Control of stress during dental procedures (human)

R01DE-04857-02 Temporalis flaps in the treatment of facial paralysis (monkeys)

** R13DE-04860-01 Conference-dental implants: benefit or risk

R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)

P50DE-04881-05 0001 Center for clinical research in periodontal diseases - Diagnosis and treatment of destructive periodontal diseases

P50DE-04881-05 0002 Center for clinical research in periodontal diseases - Relationship of subgingival microbiota to the etiology of periodontal diseases

** P50DE-04898-05 0003 Periodontal disease research center - Therapy and prevention of periodontal diseases (human)

R23DE-05155-02 Active principles of dental pulp therapeutic agents

** R01DE-05410-02 Orthodontic treatment effects on craniofacial growth (human)

R23DE-05507-02 Psychomotor impairment related to N20 exposure (human)

R23DE-05527-02 Behavioral treatments for nocturnal bruxism (human)

** R23DE-05572-02 NEW antiviral therapy for oral and other herpes (mice, guinea pig, rabbits)

P01DE-05837-01 0001 Growth, surgical, and speech aspects of cleft palate - Speech pathology (human)

** R01DE-06112-01 Filled sealant as a conservative restorative material (human)

** N01DE-82413-05 Long-term effect of orthodontic treatment

N01DE-82417-03 Effect of daily mouthrinsing with fluorides

** N01DE-92419-02 Efficacy of prior toothcleaning on fluoride treatment

THERMODYNAMICS (CHEMISTRY)

SEE CHEMISTRY, THERMODYNAMICS (GENERAL)

THERMORECEPTION

SEE SENSORY-PERCEPTUAL PROCESSES, THERMORECEPTION

THERMOREGULATION (BODY TEMPERATURE)

SEE TEMPERATURE (BODY) REGULATION

THIOCYANATES

R01DE-04235-06 Peroxidase in saliva and prevention of oral disease (human, S mutants)

THREE-DIMENSIONAL X-RAY SCANNING

SEE RADIOGRAPHY, SCANNING, DSR

THRESHOLDS, SENSORY

SEE SENSORY THRESHOLDS

THROAT

SEE ORAL-PHARYNGEAL, PHARYNX

THROMBASE

SEE BLOOD COAGULATION, THROMBIN

THROMBIN

SEE BLOOD COAGULATION, THROMBIN

THROMBOCYTES

SEE BLOOD PLATELETS

THROMBOCYTOPATHY

SEE BLOOD PLATELETS DISORDERS, THROMBOCYTOPATHY

THROMBOPATHY CONSTITUTIONAL

SEE BLOOD PLATELETS DISORDERS, THROMBOCYTOPATHY

THROMBOSIS

SEE CARDIOVASCULAR DISORDERS, THROMBOSIS

THY-1.1 ANTIGEN

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

THYMIDINE

SEE PYRIMIDINE NUCLEOSIDES, THYMINE NUCLEOSIDES, THYMIDINE

THYMUS

SEE BLOOD AND RE SYSTEM, THYMUS

THYMUS DEPENDENT IMMUNE SYSTEM

SEE IMMUNITY, CELLULAR IMMUNITY (GENERAL)

THYROCALCITONIN

SEE THYROID HORMONES, (THYR)CALCITONIN

THYROID HORMONES, (THYR)CALCITONIN

** P50DE-02668-15 0192 Regional dental research center - Skeletal actions of calcitonin in the rat

** P50DE-02668-15 0207 Regional dental research center - Effects of vitamin A and D, PTH, CT on uptake of calcium and phosphorus in enamel

R01DE-03619-09 Biochemistry of tooth eruption, movement and resorption (cats)

R01DE-04257-05 Migration and differentiation of neural crest cells (quail, chick embryo, mi)

R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)

** R01DE-05209-04 Metabolic pathways in bone

R01DE-05413-02 Bone resorption in periodontal disease

THYROTROPIN-RELEASE INHIBITING FACTOR

SEE PITUITARY-DIENCEPHALON HORMONES, SOMATOSTATIN

TI

SEE METALS, HEAVY METALS, TITANIUM (COMPOUNDS)

TIC DOLOREUX

SEE NERVOUS DISORDERS PERIPHERAL, TRIGEMINAL NEURALGIA

TIME RELEASE DRUGS

SEE DRUGS, SLOW RELEASE PREPARATIONS

TIN (COMPOUNDS)

SEE METALS, HEAVY METALS, TIN (COMPOUNDS)

TISSUE, EPITHELIUM

SEE ALSO ORAL-PHARYNGEAL, MUCOSA

P50DE-02600-15 0039 Support for oral biology research center - Saliva in abnormal bacterial adherence and colonization (human)

** P50DE-02731-15 0032 Development support for dental research institute - Epithelial cell basal lamina biosynthesis (rats)

P01DE-02848-11 0001 Biology of connective tissue, bones, and teeth - Mesenchymal interactions (mice, rabbit)

R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine

R01DE-05252-01 Bidirectional effects of subgingival dental plaque

R01DE-05586-01 Cell surface studies of the enamel organ (mice)

R01DE-05652-01 Biological role of lysozyme in human saliva

** R23DE-05887-01 Effects of oral bacteria on epithelium in vitro

TISSUE, EXOCRINE GLANDS (GENERAL)

SEE ALSO ENDOCRINOLOGY, ENDOCRINES

SEE ALSO ORAL-PHARYNGEAL, SALIVARY GLANDS

P50DE-02670-15 0018 Institute of Dental Research - Structure of human secretory immunoglobulin A

R01DE-03666-07 X-ray therapeutic index for salivary glands

R01DE-05251-02 Salivary gland secretory mechanisms (rats)

R01DE-05271-03 Neuroeffector transmission in a simple salivary gland (snails, mice)

TISSUE-BIOMATERIAL SURFACE INTERACTIONS

SEE BIOMATERIALS, INTERFACIAL PHENOMENA

TISSUE (CELL) CULTURE*

SEE ALSO PREGNANCY, EMBRYO-FETUS CULTURE

R01DE-01374-21 Matrix component interactions in calcified tissues (cattle, rats, chickens, h)

P50DE-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus

** P50DE-02623-14 0013 Center for oral health research - Mechanisms of secretory antibody induction

** P50DE-02731-15 0032 Development support for dental research institute - Epithelial cell basal lamina biosynthesis (rats)

R01DE-02774-13 Tissue interaction in palatal shelf closure (mice)

** R23DE-05332-03 Bone in vitro-Ultrastructure and autoradiography (mice)

R13DE-05752-01 Conference on biology of mineralized connective tissues

TISSUE (CELL) CULTURE, CELL CULTURE

SEE ALSO TISSUE (CELL) CULTURE, EMBRYONIC-FETAL CELL LINES

R01DE-05467-02 Pathogenesis of localized bone destruction

TISSUE (CELL) CULTURE, CLONE CELLS*

SEE ALSO NEOPLASTIC CELLS, HELA CELLS

SEE ALSO NUCLEIC ACIDS CLONING

R01DE-03258-10 Streptococcus mutans-Dental caries mechanism (human)

R01DE-05395-02 Stem cells in oral mucosa

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject

M Grant has subprojects describing specific research aspects. See Appendix for investigator's name and Grant Number.

TISSUE (CELL) CULTURE, EMBRYONIC-FETAL**CELL LINES**

SEE ALSO PREGNANCY, EMBRYO-FETUS CULTURE

- R01DE-04622-05 Craniofacial anomalies and protein receptors (mice, human)

TISSUE (CELL) CULTURE, ORGAN CULTURE

- ** R23DE-05332-03 Bone in vitro-Ultrastructure and autoradiography (mice)

TISSUE COMPATIBILITY

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOIMMUNITY

TISSUE COMPATIBILITY-TRANSPLANT, GRAFT VERSUS HOST REACTIONS

- R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)
R01DE-04489-06 Tooth transplantation genetics and immunology (mice, monkeys)

TISSUE COMPATIBILITY-TRANSPLANT, IMPLANT

- ** R01DE-05292-03 Biological prosthetic attachment (dog)
** R23DE-05883-01 Implants as anchors to move teeth and facial bones (dogs, monkeys)

TISSUE COMPATIBILITY-TRANSPLANT, IMPLANT COMPATIBILITY

- R01DE-03497-09 Artificial tooth roots (Rhesus monkeys, human)

TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

SEE ALSO IMMUNOGENETICS, HISTOCOMPATIBILITY GENES
SEE ALSO IMMUNOGENETICS, MAJOR HISTOCOMPATIBILITY COMPLEX (LOCUS)

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
P500E-02623-14 0033 Center for oral health research - Immune system in regulation of angiogenesis
R01DE-04489-06 Tooth transplantation genetics and immunology (mice, monkeys)
** R23DE-05117-03 Enhancement of oral cancer after allografting (mice)

TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOIMMUNITY

SEE ALSO TISSUE COMPATIBILITY-TRANSPLANT, GRAFT VERSUS HOST REACTIONS

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
** R01DE-04489-06 Tooth transplantation genetics and immunology (mice, monkeys)
R01DE-05563-02 The blade implant-Clinical efficacy and safety (human)

TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION

SEE ALSO BLOOD AND RE SYSTEM, BONE MARROW TRANSPLANTATION

SEE ALSO DENTAL TRANSPLANTATION

SEE ALSO MUSCLE TRANSPLANTATION

- R01DE-02212-13 Circulation in teeth and supporting structures (dogs, monkeys)
R01DE-05190-03 Factors determining variation in adult oral mucosa
** R13DE-05897-01 Oral immunogenetics and tissue transplantation (symposium)

TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION AUTOLOGOUS

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)

- ** R01DE-04857-02 Temporalis flaps in the treatment of facial paralysis (monkeys)

TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION HETEROLOGOUS

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)

TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION HOMOLOGOUS

- R01DE-02103-17 Inductive substrates of tooth and bone (rats, cattle, mice, rabbits, human)
R01DE-04489-06 Tooth transplantation genetics and immunology (mice, monkeys)

- ** R23DE-05117-03 Enhancement of oral cancer after allografting (mice)
R13DE-05897-01 Oral immunogenetics and tissue transplantation (symposium)

TISSUE CULTURE

SEE TISSUE (CELL) CULTURE*

TISSUE MOSAICISM

- R01DE-04629-05 Dental disease and osteoclastic bone resorption (chick embryo, quail)
R01DE-05616-03 Matrix-cell interaction in craniofacial development (chick embryos)

TISSUE RESPIRATION

SEE RESPIRATION INTERNAL

TITANIUM (COMPOUNDS)

SEE METALS, HEAVY METALS, TITANIUM (COMPOUNDS)

TL ANTIGEN

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

TNS STIMULATION (ELECTROANALGESIA)

SEE SENSORY DEPRESSION, ANALGESIA BY MASKING, ELECTROANALGESIA

TOLERANCESEE IMMUNITY, IMMUNOLOGICAL UNRESPONSIVENESS
SEE SENSORY-PERCEPTUAL PROCESSES, PAIN TOLERANCE**TONGUE**

SEE ORAL-PHARYNGEAL, TONGUE

TOOTH

SEE DENTAL STRUCTURE, TOOTH

TOOTH, ARTIFICIAL, ENDOSSEOUS IMPLANT

SEE DENTAL PROSTHESIS, DENTAL IMPLANT ENDOSSEOUS

TOOTH BRUSHING

SEE DENTISTRY, PREVENTIVE, TOOTH BRUSHING

TOOTH DISCOLORATION

SEE DENTAL DISCOLORATION

TOOTH DYSPLASIA, CONGENITAL

SEE CONGENITAL ABNORMALITIES, DENTITION

TOOTH ERUPTION

SEE DENTAL DEVELOPMENT

TOOTH GERM

SEE DENTAL STRUCTURE, TOOTH GERM

TOOTH LOSS

SEE DENTAL DISORDERS, TOOTH LOSS

TOOTH MOBILITY

SEE DENTAL STRUCTURE, TOOTH MOBILITY

TOOTH RESORPTION

SEE DENTAL DISORDERS, TOOTH RESORPTION

TOOTH ROOT

SEE DENTAL STRUCTURE, TOOTH ROOT

TOOTH TRANSPLANTATION

SEE DENTAL TRANSPLANTATION

TOOTH WEAR

SEE DENTAL STRUCTURE, TOOTH WEAR

TOOTHACHE

SEE DENTAL PAIN

TOPICAL APPLICATION

SEE DOSAGE AND ROUTE, TOPICAL APPLICATION

TOUCH

SEE SENSORY-PERCEPTUAL PROCESSES, TOUCH

TOXIC REACTIONS AND MECHANISMS IN IMMUNOLOGY

SEE IMMUNOLOGY, TOXIC REACTIONS AND MECHANISMS IN IMMUNOLOGY

TOXICANT METABOLISM

SEE TOXICOLOGY, TOXICANT METABOLISM

TOXICOLOGY, BACTERIAL

SEE ALSO IMMUNOLOGY, ANTIGENS BACTERIAL, BACTERIAL TOXINS (GENERAL)

- R01DE-05102-04 Potential anti-carries agents (rats)
R01DE-05696-01 Streptococcus mutans interaction with animal tissue (also human)

TOXICOLOGY, CYTOTOXICITY

SEE ALSO IMMUNOLOGICAL TESTS AND IMMUNOASSAY, AGGLUTINATION REACTION (AGGLUTININ)*

SEE ALSO IMMUNOLOGY, ANTIBODIES, AGGLUTININS

- R01DE-04096-05 Biocompatibility of endodontic materials (animals)
R01DE-04808-02 Virulence factors of gram negative corroding bacteria

- R23DE-05050-02 Sources of toxins from human dental plaque

TOXICOLOGY, EMBRYO-FETUS

SEE PREGNANCY, EMBRYO-FETUS TOXICOLOGY

TOXICOLOGY, ENVIRONMENTAL

SEE ALSO PHYSICAL AND/OR CHEMICAL AGENTS INTERACTION (BIOLOGICAL AND ECOLOGICAL)

- R01DE-05466-03 Biochemical studies of a sweetener, SRI Oxime V (rats, mice, dogs, monkeys)

TOXICOLOGY, TOXICANT METABOLISM

- ** R01DE-01850-18 0082 Nutritional sources and metabolic roles of fluoride - Nonionic fluorine in foods (human)

- ** R01DE-05466-03 Biochemical studies of a sweetener, SRI Oxime V (rats, mice, dogs, monkeys)

TOXICOLOGY, TOXICANT METABOLISM, DETOXICATION

- ** R01DE-04657-05 Abnormal palatal development induced by hadacidin (fungi)

TOXICOLOGY OF BACTERIA AND THEIR PRODUCTS

SEE TOXICOLOGY, BACTERIAL

TOXICOLOGY STUDY SECTION

- ** R01DE-05466-03 Biochemical studies of a sweetener, SRI Oxime V (rats, mice, dogs, monkeys)

TOXINS

SEE ALSO IMMUNOLOGY, ANTIGENS

SEE ALSO IMMUNOLOGY, ANTIGENS BACTERIAL

SEE ALSO IMMUNOLOGY, ANTIGENS MICROBIAL

SEE ALSO LIVER DISORDERS, TOXIC LIVER DISORDERS, HEPATOTOXINS

- ** R23DE-05050-02 Sources of toxins from human dental plaque

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SEE VIRUS CHARACTERISTICS, TRANSFORMING VIRUSES

TRANSEPITHELIAL SHUNT

SEE BIOLOGICAL TRANSPORT, MEMBRANE PERMEABILITY AND TRANSPORT

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SEE ALSO GLYCOSYLTRANSFERASES

SEE ALSO PHOSPHOTRANSFERASES

- R01DE-04321-07 Cell adherence of dental plaque forming streptococci (rabbits)

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SEE METALLOPROTEINS, TRANSFERRIN

TRANSFORMATION

SEE IMMUNITY, CELLULAR, LYMPHOCYTE ACTIVATION, TRANSFORMATION AND PROLIFERATION

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SEE NEOPLASTIC TRANSFORMATION

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SEE VIRUS CHARACTERISTICS, TRANSFORMING VIRUSES

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SEE GLYCOSYLTRANSFERASES

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SEE GENETICS, GENETIC REGULATION, GENETIC INDUCTION-REPRESSION-DEREPRESSION, TRANSLATION

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SEE ALKYL TRANSFER, TRANSMETHYLATION

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SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION

TRANSPLANTATION ANTIGENS

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOANTIGENS (HISTOCOMPATIBILITY ANTIGENS)

TRANSPLANTATION AUTOLOGOUS

SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION AUTOLOGOUS

TRANSPLANTATION HETEROLOGOUS

SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION HETEROLOGOUS

TRANSPLANTATION HOMOLOGOUS

SEE TISSUE COMPATIBILITY-TRANSPLANT, TRANSPLANTATION HOMOLOGOUS

TRANSPLANTATION IMMUNOLOGY

SEE TISSUE COMPATIBILITY-TRANSPLANT, ISOALLOIMMUNITY

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SEE BIOLOGICAL TRANSPORT, ION EXCHANGE AND TRANSPORT

SEE BIOLOGICAL TRANSPORT, MEMBRANE PERMEABILITY AND TRANSPORT

SEE KIDNEY FUNCTION, RENAL TUBULAR TRANSPORT

TRANSPORT FACILITATORS (STIMULANTS)

SEE BIOLOGICAL TRANSPORT, TRANSPORT EFFECTORS

(contd.)

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject.

M Grant has subprojects describing specific research aspects.

See Appendix for investigator's name and Grant Number.

TRANSPORT INHIBITORS

SEE BIOLOGICAL TRANSPORT, TRANSPORT EFFECTORS

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SEE BIOLOGICAL TRANSPORT, TRANSPORT PROTEINS (SEE ALSO SPECIFICS)

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SEE GENETICS, EXTRACHROMOSOMAL INHERITANCE, PLASMIDS

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SEE BACTERIA, SPIROCHETES, TREPONEMA PALLIDUM*

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SEE VITAMIN A ANALOGS

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SEE LIPIDS, GLYCERIDES, TRIGLYCERIDES

TRIAMCINOLONE

SEE ADRENAL CORTX HORMONES ANALOGS, TRIAMCINOLONE

TRIAMCINOLONE ACETONIDE

SEE ADRENAL CORTX HORMONES ANALOGS, TRIAMCINOLONE ACETONIDE

TRICARBOXYLIC ACID CYCLE

SEE TRICARBOXYLIC ACIDS, KREBS CYCLE

TRICARBOXYLIC ACIDS, KREBS CYCLE

R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism

TRIGEMINAL NERVE

SEE NERVOUS SYSTEM, CRANIAL NERVES, TRIGEMINAL NERVE

TRIGEMINAL NEURALGIA

SEE NERVOUS DISORDERS PERIPHERAL, TRIGEMINAL NEURALGIA

TRIGEMINAL NUCLEUS (SPINAL)

SEE BRAIN, PONS, TRIGEMINAL NUCLEUS (SPINAL)

TRIGLYCERIDES

SEE LIPIDS, GLYCERIDES, TRIGLYCERIDES

TRIOSE ACIDS, GLYCERIC ACID DIPHOSPHATES

R01DE-04439-04 Dental calculus formation using calcifiable lipoprotein analogues

TRIOSE ALCOHOLS, GLYCERIN

R01DE-04926-04 Bacterial coaggregation mechanisms in dental plaque

TRIPHOSPHOPYRIDINE NUCLEOTIDE(REDUCED)
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SEE CYCLIC AMINO ACIDS, TRYPTOPHAN

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SEE NUTRITION, DIET SCHEDULE AND ROUTE, TUBE FEEDING

TUBERCULIN TYPE HYPERSENSITIVITY

SEE HYPERSENSITIVITY, DELAYED HYPERSENSITIVITY

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SEE FAMILY, TWINS AND MULTIPLETS

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SEE VIRUSES, RETROVIRIDAE, LEUKOSIS-SARCOMA AVIAN, LEUKOSIS VIRUSES AVIAN

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SEE CARBOHYDRATES METABOLISM DISORDERS, DIABETES, INSULIN-DEPENDENT DIABETES

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URBAN PLANTINGS AND GREEN AREAS

SEE SOCIOENVIRONMENT, URBAN AREAS

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URETHANE POLYMERS

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URINE*

N01DE-12430-00 Investigation of anticaries vaccine in primates

URINE ACIDITY

R01DE-04332-06 Influence of acid-base status on fluoride metabolism (rats, dogs)

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V

SEE METALS, HEAVY METALS VANADIUM (COMPOUNDS)

VACCINES, BACTERIAL (GENERAL)

P50DE-02623-14 0031 Center for oral health research - Role of immunity in periodontal disease (rats)

**** R01DE-04061-07**

Salivary antibodies to S mutants-Induction and effects (monkeys)

R01DE-05352-03

Immunochemical studies in periodontal disease

VACCINES, BACTERIAL, ANTI-CARIES VACCINE**** R01DE-05359-01**

Regulation of secretory immunity to S mutants (mice)

**** R01DE-05696-01**

Streptococcus mutants interaction with animal tissue (also human)

**** N01DE-12430-00**

Investigation of anticaries vaccine in primates

VACCINES, BACTERIAL, STREPTOCOCCAL VACCINES

R01DE-02901-13 Cell wall antigens of cariogenic streptococci (human, rabbits)

R01DE-05017-03

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P50DE-02623-14 0031 Center for oral health research - Role of immunity in periodontal disease (rats)

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SEE CARDIOVASCULAR FUNCTION, BLOOD PRESSURE

VENTILATION, HEATING, AIR CONDITIONING

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VIROLOGY STUDY SECTION**** R01DE-05089-03** Oral herpes simplex-An approach to dental therapy (hamsters)**VIRULENCE MICROORGANISMS**

SEE MICROORGANISMS VIRULENCE

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SEE ALSO VIRUSES, BACTERIOPHAGE*

R01DE-05838-02 Morphogenetic role of glycosaminoglycans (chick embryo)

VIRUS DEVELOPMENT, REPLICATION

R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)

VIRUS DISEASE CHARACTERISTICS, HOST-VIRUS

R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)

VIRUS DISEASE CHARACTERISTICS, INFECTION MECHANISMS (GENERAL)

R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)

VIRUS DISEASE CHARACTERISTICS, LATENT DORMANT OR SLOW**** R01DE-05194-03** Latency of herpes simplex in oro-facial infections (human)

R23DE-05572-02 NEW antiviral therapy for oral and other herpes (mice, guinea pig, rabbits)

VIRUS DISEASES

SEE ALSO COMMUNICABLE DISEASE CONTROL AGENTS, ANTIVIRAL

SEE ALSO IMMUNOLOGY, ANTIBODIES VIRAL

SEE ALSO NEOPLASTIC TRANSFORMATION, CARCINOGENESIS, VIRAL

**** P50DE-02731-15 0038** Development support for dental research institute - Antiviral chemotherapy-Drug delivery component**VIRUS DISEASES, HERPESVIRIDAE****** R01DE-05089-03** Oral herpes simplex-An approach to dental therapy (hamsters)**VIRUS DISEASES, PARAMYXOVIRIDAE, MUMPS**

R01DE-05531-03 Salivary immune factors (human, bacteria) (cont'd).

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

VIRUS INFECTION MECHANISMS (GENERAL)

SEE VIRUS DISEASE CHARACTERISTICS, INFECTION MECHANISMS (GENERAL)

VIRUS INHIBITORS

SEE COMMUNICABLE DISEASE CONTROL AGENTS, ANTIVIRAL

VIRUS REPLICATION

SEE VIRUS DEVELOPMENT, REPLICATION

VIRUSES, BACTERIOPHAGE*

R01DE-04224-07 Genetics of oral microflora

VIRUSES, HERPESVIRIDAE, ALPHAHERPESVIRINAE

- ** P50DE-02623-14 0002 Center for oral health research - Major structural proteins of herpes simplex virus
- ** R01DE-05089-03 Oral herpes simplex--An approach to dental therapy (hamsters)
- ** R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)
- ** R01DE-05330-02 Herpes virus antibodies in patients with oral cancer
- ** R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)
- ** R23DE-05572-02 NEW antiviral therapy for oral and other herpes (mice, guinea pig, rabbits)

VIRUSES, PICORNAVIRIDAE, ENTEROVIRUS, POLIOMYELITIS VIRUS

R01DE-05194-03 Latency of herpes simplex in oro-facial infections (human)

VIRUSES, RETROVIRIDAE

R01DE-04970-04 Molecular characterization of odontogenesis by 5-bromodeoxyuridine

VIRUSES, RETROVIRIDAE, LEUKOSIS-SARCOMA AVIAN, LEUKOSIS VIRUSES AVIAN

- ** P50DE-02668-15 0176 Regional dental research center - Collagen biochemistry and the myeloblastosis associated virus infected cells

VISION

SEE EYE, VISION

VISION DISORDERS

SEE EYE DISORDERS, VISION DISORDERS

VISUAL FEEDBACK

SEE EYE, VISUAL FEEDBACK

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VITAMIN EXCESS

SEE NUTRITIONAL ABNORMALITIES, HYPERVITAMINOSIS

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- SEE ALSO NUTRITIONAL ABNORMALITIES, HYPOVITAMINOSIS A
- P50DE-02668-15 0172 Regional dental research center - Genetic and environmental factors interaction in development of cleft lip (mice)
- ** P50DE-02668-15 0207 Regional dental research center - Effects of vitamin A and D, PTH, CT on uptake of calcium and phosphorus in enamel
- P50DE-02670-15 0020 Institute of Dental Research - Nutrition--Disease proneness during dental development
- R01DE-05440-02 H-2 and teratogen-induced craniofacial malformation (mice)
- R01DE-05449-02 Transformation of oral mucosa by herpes simplex virus (hamsters)

VITAMIN A ACID

SEE VITAMIN A ANALOGS

VITAMIN A ANALOGS

R01DE-04862-04 Nutritional role of vitamin A in bone and teeth (rat)

VITAMIN A DEFICIENCY

SEE NUTRITIONAL ABNORMALITIES, HYPOVITAMINOSIS A

VITAMIN B6, PYRIDOXAL ANALOGS

R01DE-05102-04 Potential anti-caries agents (rats)

VITAMIN C

P50DE-02670-15 0020 Institute of Dental Research - Nutrition--Disease proneness during dental development

VITAMIN D DEFICIENCY

SEE NUTRITIONAL ABNORMALITIES, HYPOVITAMINOSIS D

VITAMIN D GROUP

R01DE-05209-04 Metabolic pathways in bone

VITAMIN D GROUP, VITAMIN D

- ** P50DE-02668-15 0088 Regional dental research center - Hypervitaminosis D in lactation
- ** P50DE-02668-15 0207 Regional dental research center - Effects of vitamin A and D, PTH, CT on uptake of calcium and phosphorus in enamel
- R01DE-05210-03 Acid phosphatases in developing bones and teeth (rats)
- ** R23DE-05607-02 Cells of alveolar bone during hyperparathyroidism (rats)
- R01DE-05937-01 Proteolipids and mineralization of bones and teeth (bacteria, rabbits)

VITAMIN D GROUP, VITAMIN D3 ACTIVATED

R01DE-05413-02 Bone resorption in periodontal disease
R01DE-05487-02 Kinetics of mineral recycling in teeth and bone

VITAMIN D GROUP, VITAMIN D3,25-HYDROXY-

P50DE-02668-15 0088 Regional dental research center - Hypervitaminosis D in lactation

VITAMIN D

SEE VITAMIN D GROUP, VITAMIN D

VITAMIN D3 ACTIVATED

SEE VITAMIN D GROUP, VITAMIN D3 ACTIVATED

VITAMIN D RESISTANT RICKETS

SEE KIDNEY DISORDERS, RENAL RICKETS

VITAMIN D RESISTANT RICKETS INBORN

SEE METABOLIC DISORDERS INBORN, VITAMIN D RESISTANT RICKETS INBORN

VITAMIN THERAPY

SEE NUTRITION, DIET THERAPEUTIC, VITAMIN THERAPY (ALL ROUTES OF ADMINISTRATION)

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SEE INFORMATION AND COMMUNICATION, VOICE

WATER

SEE ALSO BODY FLUID BALANCE, BODY WATER
SEE ALSO CHEMICAL REACTIONS, HYDRATION-DEHYDRATION
SEE ALSO CHEMICAL REACTIONS, SOLVOLYSIS, HYDROLYSIS
R01DE-01912-18 Tooth enamel apatite at the atomic level (human)
R01DE-05637-01 Mechanical properties of dental composite materials

WATER ENVIRONMENT, AQUATIC ORGANISMS, MARINE*

- ** R01DE-05800-01 Formation and biochemical composition of sea mussel

WATER SOLUBILITY

SEE PHYSICAL PROPERTIES, SOLUBILITY, WATER

WATER SUPPLY

R01DE-04387-05 Effect of fluoride on cAMP and glucose metabolism
R01DE-05027-04 Binding of fluoride by cariogenic bacteria
N01DE-12432-00 Caries and enamel fluoride

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R01DE-05027-04 Binding of fluoride by cariogenic bacteria

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SEE INFORMATION DISSEMINATION, MEETINGS CONFERENCES SYMPOSIA, WORKSHOP

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SEE INJURIES, WOUND HEALING

X INHERITED TRAITS

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SEE RADIOGRAPHY*

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SEE GENETIC DISORDERS, SEX-LINKED CONDITIONS

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YOUTH

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SEE METALS, RARE EARTHS, ZIRCONIUM (COMPOUNDS)

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SEE METALS, HEAVY METALS, ZINC (COMPOUNDS)

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SEE METALS, RARE EARTHS, ZIRCONIUM (COMPOUNDS)

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SEE IMMUNOLOGY, ANTIGENS MICROBIAL, ZYMOSAN

*Excludes routine methodology OR covers only general projects which preclude indexing at the specific level.

**Oriented significantly to above subject

M Grant has subprojects describing specific research aspects.
See Appendix for investigator's name and Grant Number.

INVESTIGATOR INDEX

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BELL, WILLIAM H	RO1DE03794-09	EISENMANN, DALE R	RO1DE05323-02	INGERSOLL, BARBARA	R23DE05799-01
BIRDSELL, D C	P50DE02600-15 0040	ELLISON, SOLON A	RO1DE05531-03	IORIO, ROBERT J	RO1DE05024-03
BIRDSELL, DALE C	RO1DE05991-01	ELLISON, SOLON A	NO1DE92422-04	IZUTSU, KENNETH T	P50DE02600-15 0034
BIRKEDAL-HANSEN, HE	RO1DE05817-01	ENLOW, DONALD H	RO1DE05078-05	JENSEN, OIVIND E	R23DE05042-03
BIXLER, DAVID	RO1DE05684-01	ERICKSON, CAROL A	RO1DE05630-01	JOHNSON, DORTHEA A	RO1DE06000-01
BIXLER, DAVID	RO1DE05758-01	ERICKSON, ROBERT P	RO1DE05322-01	JOHNSON, JOHN L	RO1DE05218-03
BLEIWEIS, ARNOLD S	RO1DE02901-13	EVANS, RICHARD T	RO1DE04061-07	JOHNSON, LEWIS B	RO1DE03965-08
BOACKLE, ROBERT J	RO1DE05049-01	FAIRHURST, CARL W	RO1DE04252-07	JOHNSON, RUSSELL C	RO1DE05144-03
BONICA, JOHN J	PO1DE05130-03	FAIRHURST, CARL W	RO1DE04394-05	JOHNSTON, MALCOLM C	P50DE02668-15 0172
BONICA, JOHN J	R13DE05982-01	FARBMAN, ALBERT I	RO1DE03934-07	JORDAN, HAROLD V	PO1DE02847-13 0022
BOOKSTEIN, FRED L	RO1DE05410-02	FAULKNER, JOHN A	RO1DE04857-02	JORDAN, TRUMAN H	RO1DE04192-07
BORNSTEIN, PAUL A	P50DE02600-15 0003	FELDMAN, ROY S	R23DE05332-03	JORDAN, TRUMAN H	RO1DE04705-03
BOSHILL, JERRY L	R23DE05072-03	FIELDS, HOWARD L	RO1DE05369-03	KAHN, ARNOLD J	RO1DE04629-05
BOSKEY, ADELE L	RO1DE04141-07	FILEWICH, ROBERT J	R23DE05858-01	KAMEN, PAUL R	R23DE05887-01
BOWEN, RAFAEL L	RO1DE05129-04	FINE, DANIEL H	RO1DE05252-01	KAPLAN, JEROME I	RO1DE04783-04
BOYAN-SALYERS, BARB	RO1DE05937-01	FISCHER, STEVEN C	R23DE05527-02	KATZ, J LAWRENCE	R13DE05898-01
BOYD, DALE D	NO1DE42434-21	FISHER, STANLEY E	PO1DE01697-19 0036	KAYE, C	PO1DE02872-12 0055
BRADLEY, ROBERT M	RO1DE05728-01	FIVES-TAYLOR, PAULA	RO1DE05606-02	KELLER, PATRICIA J	RO1DE05251-02
BRINKLEY, LINDA L	RO1DE02774-13	FLICSS, JOSEPH L	RO1DE04068-07	KENNY, GEORGE E	P50DE02600-15 0035
BROWN, WALTER E	RO1DE04385-06	FLYNN, GORDON L	P50DE02731-15 0038	KIM, SYNGCUK	R23DE05605-01
BROWN, WALTER E	RO1DE05354-04	FORREST, EDWARD J	PO1DE01697-19	KIMMEL, DONALD B	R23DE05607-02
BROWNELL, A G	PO1DE02848-11 0004	FOX, JEFFREY L	RO1DE04600-04	KING, GREGORY J	RO1DE04844-04
BRUNSKI, JOHN B	R23DE05418-03	FREEDMAN, MICHAEL L	RO1DE03758-07	KIYAK, H ASUMAN	RO1DE05744-01
BUGG, CHARLES E	P50DE02670-15 0001	FRETWELL, MARSHA D	P50DE02600-15 0039	KLAWITTER, JEROME J	RO1DE05292-03
BURDI, ALPHONSE R	PO1DE03610-15 0017	FREUND, THOMAS S	R23DE055316-03	KLEIN, DAVID L	NO1DE72408-06
BURK, DOROTHY T	R23DE05735-01	FULLMER, HAROLD M	P50DE02670-15	KLEIN, LEROY	RO1DE05487-02
BURSTONE, CHARLES J	RO1DE03545-09	GALE, ELLIOT N	RO1DE04358-06	KLEINBERG, ISRAEL	RO1DE03993-07
BURSTONE, CHARLES J	RO1DE03953-07	GANS, CARL	RO1DE05112-03	KLEPAC, ROBERT K	RO1DE04976-04
BURSTONE, CHARLES J	R13DE05468-01	GARANT, PHILIAS R	RO1DE03745-10	KNOX, KENNETH W	RO1DE04174-07
BURT, BRIAN A	RO1DE04504-03	GARANT, PHILIAS R	RO1DE05586-01	KORAN, ANDREW, III	RO1DE04136-07
BUTLER, WILLIAM T	P50DE02670-15 0003	GASSER, DAVID L	RO1DE05008-03	KORNMAN, KENNETH S	R23DE05599-02
BUTLER, WILLIAM T	RO1DE05092-03	GAY, THOMAS J	RO1DE04610-03	KOROSTOFF, EDWARD	RO1DE05412-02
BYERS, BENJAMIN R	RO1DE04903-03	GENCO, ROBERT J	P50DE04898-05	KOUROUIDES, THEODO	P50DE02670-15 0014
BYERS, MARGARET R	RO1DE05159-03	GENCO, ROBERT J	P50DE04898-05 0001	KOUSVELARI, ELENI E	R23DE05749-01
CAPLAN, ARNOLD I	RO1DE04008-07	GENCO, ROBERT J	P50DE04898-05 0002	KROGMAN, WILTON M	RO1DE04781-02
CAPLOW, MICHAEL	RO1DE03246-12	GENCO, ROBERT J	P50DE04898-05 0003	KROGMAN, WILTON M	RO1DE05868-01
CARLSON, DAVID S	R23DE05232-03	GENCO, ROBERT J	P50DE04898-05 0004	KURAMITSU, HOWARD K	RO1DE03258-10
CARR, C W	PO1DE01850-18 0072	GENCO, ROBERT J	R13DE05753-01	KURAMITSU, HOWARD K	RO1DE05141-03
CEDERQUIST, K ROBER	R23DE05627-02	GENTRY, GLENN A	RO1DE05089-03	KUSY, ROBERT P	P50DE02668-15 0123
CERKLEWSKI, FLORIAN	R23DE05628-02	GERMAINE, GREG R	RO1DE05652-01	LALLY, EDWARD T	RO1DE05414-02
CHAPMAN, C RICHARD	RO1DE04004-07	GHERNA, ROBERT L	NO1DE92418-05	LANDIS, WILLIAM J	RO1DE05351-02
CHARON, NYLES W	RO1DE04645-04	GIBBONS, RONALD J	PO1DE02847-13	LANGDON, HERBERT L	PO1DE01697-19 0038
CHRISTNER, PAUL	P50DE02623-14 0027	GIBBONS, RONALD J	PO1DE02847-13 0020	LANGELAND, KAARE	RO1DE04096-05
CLAGETT, JAMES A	P50DE02600-15 0014	GIBBS, CHARLES H	RO1DE04157-08	LASKIN, DANIEL M	RO1DE05679-01
CLARK, GLENN T	R23DE05036-03	GLASER, ELLEN R	PO1DE01697-19 0037	LAVEN, GEORGE T	R23DE05006-03
CLARK, ROBERT W, JR	R23DE05310-03	GOLD, H O	PO1DE02872-12 0053	LE DOUARIN, NICOLE	RO1DE04257-05
CLARK, WILLIAM B	R23DE05429-03	GOLDBERG, A JON	RO1DE05321-02	LEBLOND, CHARLES P	RO1DE05690-01
CLARKSON, BRIAN H	RO1DE04835-03	GOLDMAN, ALLEN S	RO1DE04622-05	LEINFELDER, KARL F	P50DE02668-15 0191
CLEWELL, DON B	P50DE02731-15 0019	GOLDMAN, ALLEN S	RO1DE05041-03	LEINFELDER, KARL F	RO1DE04101-07
COBURN, ROBERT A	RO1DE04744-04	GOLDSTINE, STEVEN N	R23DE05789-01	LEONARD, MYER S	RO1DE05582-01
COFFEY, JAMES C	P50DE02668-15 0213	GOLUB, LORNE M	RO1DE03987-07	LEVERETT, DENNIS H	NO1DE72407-07
COHEN, GARY H	P50DE02623-14 0002	GOODMAN, MURRAY	RO1DE05476-02	LEVERETT, DENNIS H	NO1DE82417-03
COHN, DAVID V	RO1DE05209-04	GOODSON, J MAX	P50DE04881-05 0004	LEVINE, MARTIN	R23DE05050-02
CONVERSE, JOHN M	PO1DE03568-07	GOODSON, JO M	RO1DE05334-02	LEVINE, MICHAEL J	RO1DE04518-06
COOK, CLARENCE E	NO1DE02428-04	GRABER, THOMAS M	RO1DE05307-03	LEVINE, MICHAEL J	RO1DE04971-03
CORAH, NORMAN L	RO1DE04494-05	GREENE, ROBERT M	RO1DE05550-01	LEVY, RICHARD A	RO1DE05390-03
COWMAN, RICHARD A	RO1DE04278-06	GWINNETT, A JOHN	RO1DE05137-03	LILJEMARK, WILLIAM	RO1DE04614-05
COYKENDALL, ALAN L	RO1DE04721-04	HABER, JEROME	R23DE05240-03	LINDHE, JAN T	RO1DE04890-03
		HACKNEY, JOHN F	RO1DE05168-03	LINZER, ROSEMARY	RO1DE05017-03

ALPHABETICAL LISTING OF INVESTIGATORS

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LISTGARTEN, MAX A	P50DE02623-14 0009	OFFENBACHER, STEVEN	R23DE05967-01	SESSLE, BARRY J	R01DE04786-04
LOESCHE, WALTER J	P50DE02731-15 0021	OKABE, TORU	R01DE04262-07	SHAPIRO, EVERETT	R01DE04487-05
LONG, ROSS E, JR	R23DE05942-01	OPDERBECK, WILLIAM	R01DE04335-05	SHAPIRO, IRVING M	P50DE02623-14 0030
LOPATIN, DENNIS E	P50DE02731-15 0035	OPHAUG, ROBERT H	P01DE01850-18 0075	SHAW, ROBERT E	R01DE04990-03
LOPATIN, DENNIS E	R01DE05723-01	OPHAUG, ROBERT H	P01DE01850-18 0087	SHEARER, THOMAS R	R01DE03856-07
LUBEN, RICHARD A	R01DE05467-02	OPHAUG, ROBERT H	P01DE01850-18 0089	SHEARER, THOMAS R	R01DE04616-04
LUNDBLAD, ROGER L	P50DE02668-15 0152	PABST, MICHAEL J	R01DE05494-02	SHEETZ, JAMES H, JR	R23DE05142-03
LUNDBLAD, ROGER L	P50DE02668-15 0190	PAGE, ROY C	P50DE02600-15	SHILLITOE, EDWARD J	R01DE05330-02
LURIE, ALAN G	R01DE03996-06	PAGE, ROY C	P50DE02600-15 0041	SHIOTA, TETSUO	P50DE02670-15 0025
LUSCHEI, ERICH S	R01DE04884-13	PAGE, ROY C	P50DE02600-15 9001	SHIOTA, TETSUO	N01DE62491-12
MABIE, CURTIS P	R01DE05353-04	PAGE, ROY C	R01DE03301-11	SHOCKMAN, GERALD D	R01DE03487-10
MACCALLUM, DONALD K	P50DE02731-15 0032	PARADISE, JACK L	P01DE01697-19 0039	SIEGEL, IVENS A	R01DE05678-02
MACEDO-SOBRINHO, BR	R01DE04501-06	PARK, BYUNG H	R01DE05505-02	SIEGEL, MICHAEL I	P01DE01697-19 0040
MACKENZIE, IAN C	R01DE05190-03	PARK, NO HEE	R23DE05572-02	SILVERSTONE, LEON M	R01DE04819-05
MACKENZIE, IAN C	R01DE05395-02	PARMLEY, RICHARD T	P50DE02670-15 0035	SIMMELINK, JAMES W	R01DE02525-16
MACRINA, FRANCIS L	R01DE04224-07	PARRIS, PAMELA	R01DE02872-12 0056	SIMMONS, DAVID J	R01DE05109-02
MAHLER, DAVID B	R01DE02320-16	PASHLEY, DAVID H	R01DE03780-09	SIMPSON, WAITS A	R01DE05773-01
MAHLER, DAVID B	R01DE02936-13	PASK, JOSEPH A	R01DE05460-02	SINGER, LEON	P01DE01850-18
MALAMUD, D	P50DE02623-14 0032	PATTERS, MARK R	R23DE05331-01	SINGER, LEON	P01DE01850-18 0068
MALAMUD, DANIEL F	R01DE05462-01	PERTSCHUK, MICHAEL	R01DE05371-01	SINGER, LEON	P01DE01850-18 0071
MANDEL, IRWIN D	R01DE01554-20	PETERSON-FALZONE, S	P01DE02872-12 0057	SINGER, LEON	P01DE01850-18 0081
MANDELL, ROBERT L	R23DE05591-01	PHILLIPS, CEIG L	R01DE05698-01	SINGER, LEON	P01DE01850-18 0082
MANSHEIM, BERNARD J	R01DE05352-03	PIERINGER, RONALD A	R01DE04957-03	SINGER, LEON	P01DE01850-18 0084
MAREK, MIROSLAV	R01DE03601-09	PLISKIN, MICHAEL E	P50DE02623-14 0033	SINGER, LEON	P01DE01850-18 0085
MARKS, SANDY C, JR	R01DE03818-08	PLISKIN, MICHAEL E	R23DE05117-03	SINGER, LEON	P01DE01850-18 0086
MARKS, SANDY C, JR	R01DE05996-01	POLLOCK, JERRY J	R01DE04296-07	SINGER, LEON	P01DE01850-18 0088
MARSHALL, SALLY J	R01DE04704-05	POLSON, ALAN M	N01DE82413-05	SKOBE, ZIEDONIS	R01DE04230-07
MARTINEZ, J RICARDO	R01DE04897-02	POTTER, ROSARIO H	R01DE05669-01	SLAVKIN, HAROLD C	P01DE02848-11
MAY, PAUL D	R01DE04814-02	POTTER, ROSARIO H	R01DE05771-01	SLAVKIN, HAROLD C	P01DE02848-11 0001
MAYER, ROBERT M	R01DE03731-06	PROFFIT, WILLIAM R	R01DE05198-02	SLAVKIN, HAROLD C	P01DE02848-11 0002
MC CABE, MEAD M	R01DE04321-07	PROFFIT, WILLIAM R	R01DE05215-03	SLAVKIN, HAROLD C	P01DE02848-11 0003
MC CALL, WILLARD D,	R01DE04889-04	PRUZANSKY, P	P01DE02872-12 0018	SLEE, ANDREW M	R01DE04808-02
MC CLURE, HAROLD M	N01DE52452-12	PRUZANSKY, SAMUEL	P01DE02872-12	SLOMIANY, BRONISLAW	R01DE05666-01
MC GHEE, JERRY R	R01DE04217-07	PRUZANSKY, SAMUEL	P01DE02872-12 0034	SMITH, CHARLES E	R23DE05424-03
MC INTIRE, FLOYD C	R01DE04926-04	PRUZANSKY, SAMUEL	P01DE02872-12 0035	SMITH, ERIC E	R01DE03118-11
MC KENNA, THOMAS W	N01DE92421-14	PRUZANSKY, SAMUEL	P01DE02872-12 0036	SNYDERMAN, RALPH	R01DE03738-09
MC NAMARA, JAMES A,	R01DE04227-07	PRUZANSKY, SAMUEL	P01DE02872-12 0037	SOCRANSKY, SIGMUND	P01DE02847-13 0023
MCCARTHUR, WILLIAM P	P50DE02623-14 0023	PRUZANSKY, SAMUEL	P01DE02872-12 0038	SOCRANSKY, SIGMUND	R01DE03488-10
MCCARTHY, JOSEPH G	P01DE03568-07 0008	PRUZANSKY, SAMUEL	P01DE02872-12 0061	SOCRANSKY, SIGMUND	P50DE04881-05
MCCARTHY, JOSEPH G	P01DE03568-07 0009	PRUZANSKY, SAMUEL	P01DE02872-12 0062	SOCRANSKY, SIGMUND	P50DE04881-05 0001
MCCARTHY, JOSEPH G	P01DE03568-07 0013	PRUZANSKY, SAMUEL	P01DE02872-12 0063	SOCRANSKY, SIGMUND	P50DE04881-05 0002
MC GHEE, JERRY R	P50DE02670-15 0037	PRUZANSKY, SAMUEL	P01DE02872-12 9001	SODICOFF, MARVIN	R01DE03666-07
MCNAMARA, JAMES A	P01DE03610-15 0018	PUTNEY, JAMES W, JR	R01DE05764-02	SOLBERG, WILLIAM K	R01DE05381-01
MECHANIC, GERALD L	P50DE02668-15 0125	RAMFJORD, SIGURD P	P50DE02731-15 0033	SPECTOR, MYRON	R01DE04414-06
MECHANIC, GERALD L	P50DE02668-15 0176	RANNEY, RICHARD R	R01DE05054-03	SQUIER, CHRISTOPHER	R01DE05525-02
MEIER, STEPHEN P	R01DE05616-03	RANNEY, RICHARD R	P50DE05139-04	STAAT, ROBERT H	R01DE05427-01
MELAMED, BARBARA G	R01DE05305-02	RANNEY, RICHARD R	P50DE05139-04 0001	STANFORD, JOHN W	R01DE05411-02
MELLBERG, JAMES R	N01DE12431-00	RANNEY, RICHARD R	P50DE05139-04 0002	STARR, PHILIP	R01DE04779-04
MELLBERG, JAMES R	N01DE12432-00	RANNEY, RICHARD R	P50DE05139-04 0003	STASHANKO, PHILIP	P50DE04881-05 0003
MELNICK, MICHAEL	R01DE05440-02	RAWLS, HENRY R	R01DE05596-02	STASHENKO, PHILIP	R01DE05747-01
MERTZ-FAIRHURST, EV	R01DE06112-01	REED-MILLER, CHARLE	R23DE05491-02	STINSON, MURRAY W	R01DE05696-01
MESSER, HAROLD H	R01DE04475-03	REED, MICHAEL J	R01DE05732-02	STODL, SYLVAN E	P01DE01697-19 0041
MESTECKY, JIRI F	P50DE02670-15 0018	REISINE, SUSAN T	R23DE05497-02	STORB, URSULA B	P50DE02600-15 0023
MEYER, MAURICE W	R01DE02212-13	REITH, EDWARD J	R01DE05769-03	STUCHELL, ROBERT N	R23DE05777-01
MILLER, ARTHUR J	R01DE04940-04	RETIEF, D HUGO	P50DE02670-15 0036	STUPP, SAMUEL I	R23DE05945-01
MILLER, EDWARD J	P50DE02670-15 0019	RIPA, LOUIS W	N01DE92419-02	SULIK, KATHLEEN M	P50DE02668-15 0212
MILLER, MARILYN	P01DE02872-12 0058	RIVIERE, GEORGE R	R01DE04489-06	SUTTER, VERA L	R01DE05560-01
MINAH, GLENN E	R01DE04795-05	RIVIERE, GEORGE R	R01DE05359-01	TAICHMAN, LORNE B	R01DE04511-06
MINKOFF, ROBERT	R01DE04731-05	ROBERTS, W EUGENE	R01DE05136-03	TAICHMAN, NORTON S	R01DE03995-07
MITDMA, CHOZO	R01DE05466-03	ROBERTSON, PAUL B	R01DE05706-01	TAMARIN, ARNOLD	R01DE05138-03
MOFFETT, BENJAMIN C	R01DE05379-01	ROBYT, JOHN F	R01DE05378-10	TAUBMAN, MARTIN A	R01DE053420-09
MONTGOMERY, PAUL C	P50DE02623-14 0013	RODAN, GIDEON A	R01DE04327-06	TEITELBAUM, STEVEN	R01DE05413-02
MOORE, PAUL A	R23DE05507-02	RODEN, LENNART	P50DE02670-15 0024	THOMAS, EDWIN L	R01DE04235-06
MOORREES, COENRAAD	R01DE02783-14	ROSAN, BURTON	P50DE02623-14 0014	TOOLE, BRYAN P	R01DE05388-02
MOOSER, GREGORY	R01DE03739-09	ROSAN, BURTON	R01DE03180-11	TOVERUD, S U	P50DE02668-15 0088
MORENO, EDGARDO C	R01DE03187-10	ROSENBLUM, JOEL	P50DE02623-14	TOVERUD, SVEIN U	R01DE05210-03
MORRIS, HUGHLETT L	P01DE05837-01	ROSENBLUM, JOEL	P50DE02623-14 0026	TURLEY, PATRICK K	R23DE05883-01
MORRIS, HUGHLETT L	P01DE05837-01 0002	ROSENFELD, JOEL P	R01DE05204-03	TURNER, DEREK T	P50DE02668-15 0149
MORRIS, HUGHLETT L	P01DE05837-01 0003	ROSSOMANDO, EDWARD	R01DE03715-06	TURNER, DEREK T	P50DE02668-15 0150
MORRIS, HUGHLETT L	P01DE05837-01 0004	ROSSOMANDO, EDWARD	R01DE04657-05	TYAN, MARVIN L	R01DE05165-03
MOSS, MELVIN L	R01DE05145-03	ROWLATT, V	P01DE02872-12 0059	TZORTZATOU, GEORGIA	R23DE05592-02
MOYERS, ROBERT E	P01DE03610-15	RUTHERFORD, R BRUCE	R01DE05512-02	UITTO, VELI-JUKKA V	R23DE05793-01
MOYERS, ROBERT E	P01DE03610-15 0016	RYAN, VIVIAN W	R01DE05436-03	URIST, MARSHALL R	R01DE02103-17
MUHL, ZANE F	R01DE04164-06	RYGE, GUNNAR	R01DE04516-03	VAIDYANATHAN, TRITA	R23DE05314-03
NAHMAS, ANDRE J	R01DE05194-03	SADOWSKY, DONALD	R01DE05622-01	VANHOUTE, JOHANNES	P01DE02847-13 0021
NANCOLLAS, GEORGE H	R01DE03223-11	SAKAMOTO, SEIZABURO	R01DE05255-03	VARGERVIK, KARIN	R01DE05558-01
NANDA, RAVINDRA	R01DE05396-02	SCHACHTELE, CHARLES	R01DE03654-09	VEIS, ARTHUR	R01DE01374-21
NATIELLA, JOSEPH R	R01DE03991-06	SCHENKEIN, HARVEY A	R01DE05626-01	VEIS, ARTHUR	R13DE05752-01
NAVIA, JUAN M	P50DE02670-15 0020	SCHNEIDER, GARY B	R01DE06065-01	VIG, PETER S	R01DE05203-03
NAVIA, JUAN M	R01DE04862-04	SCHNEIR, MICHAEL L	R01DE03318-10	VITTEK, JOZEF	R01DE04039-04
NEXT	P01DE05837-01 0001	SCHNEYER, CHARLOTTE	R01DE02110-17	VOGEL, JAMES J	R01DE04439-04
NISEGARD, RUSSELL	R01DE03408-09	SCHNITMAN, PAUL A	R13DE04860-01	WAITE, JOHN H	R23DE05956-01
NOT AVAILABLE	N01DE12434-00	SCHNITMAN, PAUL A	R01DE05563-02	WALKER, CLAY B	R01DE06070-01
NOWOTNY, ALOIS H	P50DE02623-14 0031	SCHRAER, HARALD	R01DE04345-06	WARREN, DONALD W	P50DE02668-15 0214
O'BRIEN, WILLIAM J	R01DE05423-02	SCHUSTER, GEORGE S	R01DE05449-02	WATERMAN, ROBERT E	R01DE05367-02
O'BRIEN, W J	P50DE02731-15 0037	SCHWARTZ, STEPHEN A	R01DE04970-04	WATERMAN, ROBERT E	R01DE05555-01
OCCHINO, JOSEPH C	R01DE04338-06	SENSEMAN, DAVID M	R01DE05271-03	WATSON, ANN Y	R23DE05985-01

WATSON, EILEEN L
 WEBER, DENNIS F
 WEFEL, JAMES S
 WEINSTEIN, SAM
 WESTON, JAMES A
 WHANGER, PHILIP D
 WHISTLER, ROY L
 WHITE, GILBERT C

R01DE05249-02
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WHITFORD, GARY M
 WHITFORD, GARY M
 WHITSEL, BARRY L
 WHITSEL, BARRY L
 WHITSEL, BARRY L
 WICKEN, ANTHONY J
 WILLIAMS, BETSY L
 WISOTZKY, JOEL

R01DE04332-06
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WOLKE, IRA
 YOTIS, WILLIAM W
 YOUNG, FRANKLIN A,
 YOUNG, ROBERT A
 YOUNG, RONALD F
 YU, JIA-HUEY
 ZIMMERMAN, ERNEST F
 P01DE02872-12 0060
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 R01DE03469-10

G L O S S A R Y O F A B B R E V I A T I O N S

GLOSSARY OF ABBREVIATIONS

The mechanism of support can be determined from the prefix (Activity Code) of the project numbers as follows:

P01	Research Program Project
P50	Dental Research Institute Program
R01	Research Projects
R13	Research Conferences
R23	Special Research Award Program
N01	Research Contract
Y01	Interagency Agreement
Z01	Intramural Research Project

A four-digit number following the project number indicates a subproject of a larger grant.

INITIAL REVIEW GROUPS 1/

<u>Code</u>	<u>Name</u>	<u>Organization</u>
AFY	Applied Physiology and Orthopedic Study Section	DRG
AGE	Aging Review Committee	NIA
AIRC	Allergy and Immunology Research Committee	NIAID
ALC	Alcohol Research Review Committee	NIAAA
ALCB	Alcohol Biomedical Research Review Committee	NIAAA
ALCP	Alcohol Psychosocial Research Review Committee	NIAAA
ALP	Alcohol Abuse Prevention Review Committee	NIAAA
ALT	Alcohol Human Resources Development Review Committee	NIAAA
ALY	Allergy and Immunology Study Section	DRG
AMLS	Automation in the Medical Laboratory Sciences Review Committee	NIGMS
AMRA	Human Resources and Research Review Group A	NIAMDD
AMRB	Human Resources and Research Review Group B	NIAMDD
AMSA	Special Projects Review Group A	NIAMDD
AMSB	Special Projects Review Group B	NIAMDD
AMSC	Special Projects Review Group C	NIAMDD
AR	Animal Resources Review Committee	DRR
ASRB	Special Review Committee - Public Inebriate; Drinking Driver; Poverty Alcoholism; Demonstrations, Surveys	NIAAA
ASRO	Special Review Committee - Occupational Alcoholism	NIAAA
ASRP	Special Review Committee - Community Prevention; Youth Education	NIAAA
BBCA	Biophysics and Biophysical Chemistry A Study Section	DRG
BBCB	Biophysics and Biophysical Chemistry B Study Section	DRG
BBP	Basic Behavioral Processes Research Review Committee	NIMH
BCE	Biochemical Endocrinology Study Section	DRG
BEM	Behavioral Medicine Review Group (AHR) [formerly assigned as EDC(AHR)]	DRG
BES	Behavioral Sciences Review Group (AHR) [formerly assigned as SSP(AHR)]	DRG
BIA	Biomedical Sciences Review Group A	DRG
BIB	Biomedical Sciences Review Group B	DRG
BIC	Biomedical Sciences Review Group C	DRG
BID	Biomedical Sciences Review Group D	DRG
BIO	Biochemistry Study Section	DRG
BLR	Biomedical Library Review Committee	NLM
BLS	Biological Sciences Training Committee	NIMH
BM	Bacteriology and Mycology Study Section	DRG
BMT	Metallobiochemistry Study Section	DRG
BNP	Bio-organic and Natural Products Chemistry Review Group (AHR) [formerly assigned as MCHA(AHR)]	DRG
BNSA	Behavioral and Neurosciences Review Group A	DRG
BNSB	Behavioral and Neurosciences Review Group B	DRG
BNSC	Behavioral and Neurosciences Review Group C	DRG
BNSD	Behavioral and Neurosciences Review Group D	DRG
BNSE	Behavioral and Neurosciences Review Group E	DRG

1/ Reflects IRG codes assigned to competing applications in the IMPAC System since 1976.

INITIAL REVIEW GROUPS (continued) 1/

<u>Code</u>	<u>Name</u>	<u>Organization</u>
BPNA	Basic Psychopharmacology and Neuropsychology Research Review Committee - Basic Psychopharmacology Subcommittee	NIMH
BPNB	Basic Psychopharmacology and Neuropsychology Research Review Committee - Neuropsychology Subcommittee	NIMH
BPO	Bio-Psychology Study Section	DRG
BSR	Basic Sociocultural Research Review Committee	NIMH
CAK	Cancer Special Program Advisory Committee	NCI
CAP	Cancer Research Center Review Committee	NCI
CAS	Community Alcoholism Services Review Committee	NIAAA
CASA	Community Alcoholism Services Review Committee - American Indian and Alaskan Native Alcoholism Services Review Subcommittee	NIAAA
CASB	Community Alcoholism Services Review Committee - Treatment and Occupational Subcommittee	NIAAA
CBY	Cell Biology Study Section	DRG
CCG	Cancer Control Grant Review Committee	NCI
CCI	Cancer Clinical Investigation Review Committee	NCI
CCP	Clinical Cancer Program Project Review Committee	NCI
CCS	Cancer Center Support Grant Review Committee	NCI
CD	Crime and Delinquency Review Committee	NIMH
CDR	Communicative Disorders Review Committee	NINCDS
CEC	Clinical Cancer Education Committee	NCI
CEP	Cognition, Emotion, and Personality Research Review Committee	NIMH
CET	Continuing Education Training Review Committee	NIMH
CLNA	Clinical Sciences Review Group A	DRG
CLNB	Clinical Sciences Review Group B	DRG
CLNC	Clinical Sciences Review Group C	DRG
CLND	Clinical Sciences Review Group D	DRG
CLR	General Clinical Research Centers Committee	DRR
CLTR	Clinical Trials Review Committee	NHLBI
CMBD	Cellular and Molecular Basis of Disease Review Committee	NIGMS
CMS	Communicative Sciences Study Section	DRG
COM	Computer and Biomathematical Sciences Study Section	DRG
CP	Cellular Physiology Review Group (AHR) [formerly assigned as CBY(AHR)]	DRG
CPA	Chemical Pathology Study Section	DRG
CPP	Clinical Psychopharmacology Research Review Committee	NIMH
CPR	Clinical Projects Research Review Committee	NIMH
CPS	Community Processes and Social Policy Review Committee	NIMH
CRC	Construction Review Committee	BHP

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INITIAL REVIEW GROUPS (continued) 1/

<u>Code</u>	<u>Name</u>	<u>Organization</u>
CT	Cancer Institutional Fellowship Review Committee	NCI
CTY	Molecular Cytology Study Sections	DRG
CUAN	Mental Health Cultural Anthropology Review Committee	NIMH
CVA	Cardiovascular and Pulmonary Study Section	DRG
CVB	Cardiovascular and Renal Study Section	DRG
CVRA	Criminal and Violent Behavior Review Committee - Crime and Delinquency Subcommittee	NIMH
CVRB	Criminal and Violent Behavior Review Committee - Sexual Assault Subcommittee	NIMH
DABR	Drug Abuse Biomedical Research Review Committee	NIDA
DACB	Drug Abuse Clinical, Behavioral, and Psychosocial Research Review Committee	NIDA
DARD	Drug Abuse Resource Development Review Committee	NIDA
DAT	Drug Abuse Training Review Committee	NIDA
DBR	Developmental Behavioral Sciences Study Section	DRG
DPE	Drug Abuse Prevention and Education Review Committee	NIDA
DSR	Dental Research Institute Review Committee	NIDR
ECS	Experimental Cardiovascular Sciences Review Group (AHR) [formerly assigned as CVB(AHR)]	DRG
EDC	Epidemiology and Disease Control Study Section	DRG
EH	Blood Research Review Group (AHR) [formerly assigned as HEM(AHR)]	DRG
EI	Experimental Immunology Review Group (AHR) [formerly assigned as ALY(AHR)]	DRG
END	Endocrinology Study Section	DRG
EPR	Experimental Psychology Research Review Committee	NIMH
EPSA	Epidemiologic and Services Research Review Committee - Epidemiology and Quantitative Services Subcommittee	NIMH
EPSB	Epidemiologic and Services Research Review Committee - Services Improvement, Evaluation, and Knowledge Transfer Research Subcommittee	NIMH
ESR	Epidemiologic Studies Review Committee	NIMH
ET	Experimental Therapeutics Study Section	DRG
EVR	Experimental Virology Study Section	DRG
EXP	Experimental Psychology Study Section	DRG
EXT	Experimental and Special Training Review Committee	NIMH

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INITIAL REVIEW GROUPS (continued) 1/

<u>Code</u>	<u>Name</u>	<u>Organization</u>
GBD	Genetic Basis of Disease Review Committee	NIGMS
GCN	Gastroenterology and Clinical Nutrition Review Group (AHR) [formerly assigned as GMA(AHR)]	DRG
GEN	Genetics Study Section	DRG
GMA	General Medicine A Study Section	DRG
GMB	General Medicine B Study Section	DRG
GRS	General Research Support Program Review Committee	DRR
HCT	Health Care Technology Study Section	NCHSR
HDMC	Maternal and Child Health Research Committee	NICHD
HDMR	Mental Retardation Research and Training Committee	NICHD
HDPR	Child Health Population Research and Training Committee	NICHD
HED	Human Embryology and Development Study Section	DRG
HEM	Hematology Study Section	DRG
HEPA	Heart, Lung, and Blood Research Review Committee A	NHLBI
HEPB	Heart, Lung, and Blood Research Review Committee B	NHLBI
HLBA	Heart, Lung, and Blood Research Review Committee A	NHLBI
HLBB	Heart, Lung, and Blood Research Review Committee B	NHLBI
HSDG	Health Services Developmental Grants Study Section	NCHSR
HSR	Health Services Research Study Section	NCHSR
HUD	Human Development Study Section	DRG
IAC	International Advisory Committee	FIC
IDC	Infectious Disease Committee	NIAID
IMB	Immunobiology Study Section	DRG
IMS	Immunological Sciences Study Section	DRG
IRRP	International Research Review Panel	FIC
JP	Developmental Problems Research Review Committee	NIMH
LCRA	Life Course Research Review Committee - Child and Family Subcommittee	NIMH
LCRB	Life Course Research Review Committee - Aging Subcommittee	NIMH
MB	Microbiology Review Group (AHR) [formerly assigned as BM(AHR)]	DRG
MBC	Microbial Physiology Study Section	DRG
MBY	Molecular Biology Study Section	DRG
MCHA	Medicinal Chemistry A Study Section	DRG
MCHB	Medicinal Chemistry B Study Section	DRG
MCL	Mammalian Cell Line Committee	NIGMS
MET	Metabolism Study Section	DRG
MG	Microbial Genetics Review Group (AHR) [formerly assigned as MBC(AHR)]	DRG

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INITIAL REVIEW GROUPS (continued) 1/

<u>Code</u>	<u>Name</u>	<u>Organization</u>
MGH	Mammalian Genetics Study Section	DRG
MHK	Research Scientist Development Review Committee	NIMH
MHP	Clinical Program Projects Research Review Committee	NIMH
MHS	Mental Health Services Research Review Committee	NIMH
MID	Microbiology and Infectious Diseases Advisory Committee	NIAID
MN	Minority Group Mental Health Review Committee	NIMH
MP	Metropolitan Mental Health Problems Review Committee	NIMH
MR	Research Manpower Review Committee	NHLBI
MRC	Minority Access to Research Careers Review Committee	NIGMS
MSM	Mental Health Small Grant Committee	NIMH
MSMA	Mental Health Small Grant Review Committee - Social and Clinical Sciences Subcommittee	NIMH
MSMB	Mental Health Small Grant Review Committee - Laboratory Experimental and Physiological Subcommittee	NIMH
HAD	Drug Abuse Research Review Committee	NIDA
NCR	No Committee Review	
NEUA	Neurology A Study Section	DRG
NEUB	Neurology B Study Section	DRG
NLS	Neurological Sciences Study Section	DRG
NP	Neuropsychology Research Review Committee	NIMH
NRE	Nursing Research and Education Advisory Committee	BHP
NSPA	Neurological Disorders Pgm. Project Review A Committee	NINCDS
NSPB	Neurological Disorders Pgm. Project Review B Committee	NINCDS
NSS	No Initial Review Group	
NTN	Nutrition Study Section	DRG
NUR	Mental Health Nursing Committee	NIMH
OBM	Oral Biology and Medicine Study Section	DRG
PB	Physical Biochemistry Review Group (AHR) [formerly assigned as BIO(AHR)]	DRG
PBC	Pathobiological Chemistry Study Section	DRG
PC	Physiological Chemistry Study Section	DRG
PCBA	Psychopathology and Clinical Biology Research Review Committee - Clinical Psychopathology Subcommittee	NIMH
PCBB	Psychopathology and Clinical Biology Research Review Committee - Clinical Biology Subcommittee	NIMH

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INITIAL REVIEW GROUPS (continued) 1/

<u>Code</u>	<u>Name</u>	<u>Organization</u>
PCR	Personality and Cognition Research Committee	NIMH
PGR	Nurse Training Project Grants Review Committee	BHP
PHRA	Pharmacology Study Section	DRG
PHY	Physiology Study Section	DRG
PI	Psychiatry Education Review Committee	NIMH
PME	Primate Research Centers Advisory Committee	DRR
PNE	Psychiatric Nursing Education Review Committee	NIMH
PO	Psychology Education Review Committee	NIMH
POP	Population Research Study Section	DRG
PPD	Paraprofessional Education Review Committee	NIMH
PPR	Preclinical Psychopharmacology Research Review Committee	NIMH
PS	Psychological Sciences Fellowship Committee	NIMH
PTHA	Pathology A Study Section	DRG
PTHB	Pathology B Study Section	DRG
PTR	Pharmacology - Toxicology Review Committee	NIGMS
RAD	Radiation Study Section	DRG
REB	Reproductive Biology Study Section	DRG
RERA	Mental Health Research Education Review Committee - Biological and Neurosciences Subcommittee	NIMH
RERB	Mental Health Research Education Review Committee - Psychological Sciences Subcommittee	NIMH
RERC	Mental Health Research Education Review Committee - Social Problems and Social Sciences Subcommittee	NIMH
RNM	Diagnostic Radiology Study Section	DRG
SAT	Surgery, Anesthesiology and Trauma Study Section	DRG
SB	Surgery and Bioengineering Study Section	DRG
SGYA	Surgery A Study Section	DRG
SGYB	Surgery B Study Section	DRG
SMDA	Mental Health Services Manpower Development Review Committee - State Manpower Development Subcommittee	NIMH
SMDB	Mental Health Services Manpower Development Review Committee - Mental Health Training R&D Subcommittee	NIMH
SOH	Safety and Occupational Health Study Section	NIOSH
SP	Mental Health Social Problems Research Review Committee	NIMH
SRC	Special Review Committee (all Institutes)	
SS	Mental Health Social Sciences Training Committee	NIMH
SSP	Social Sciences and Population Study Section	DRG
SSR	Social Sciences Research Review Committee	NIMH
SSS	Special Study Section	DRG
STC	Special Training Review Committee (all Institutes)	
SWE	Social Work Education Review Committee	NIMH

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INITIAL REVIEW GROUPS (continued) 1/

<u>Code</u>	<u>Name</u>	<u>Organization</u>
TDAA	Treatment Development and Assessment Research Review Committee - Psychosocial and Biobehavioral Treatments Subcommittee	NIMH
TDAB	Treatment Development and Assessment Research Review Committee - Psychopharmacological, Biological and Physical Treatments Subcommittee	NIMH
TDAC	Treatment Development and Assessment Research Review Committee - Clinical Program Projects and Clinical Research Centers Subcommittee	NIMH
TIC	Transplantation Immunology Committee	NIAID
TMP	Tropical Medicine and Parasitology Study Section	DRG
TOX	Toxicology Study Section	DRG
VID	Visual Disorders Review Group (AHR) [formerly assigned as VISA(AHR)]	DRG
VISA	Visual Sciences A Study Section	DRG
VISB	Visual Sciences B Study Section	DRG
VR	Virology Study Section	DRG
VSN	Vision Research Program Committee	NEI

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